(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/75337 A1

(51) International Patent Classification[7]: C12N 15/51, C07K 14/18, C12Q 1/68, C12N 7/00

(21) International Application Number: PCT/US00/15293

(22) International Filing Date: 2 June 2000 (02.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/137,694 4 June 1999 (04.06.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/137,694 (CON)
Filed on 4 June 1999 (04.06.1999)

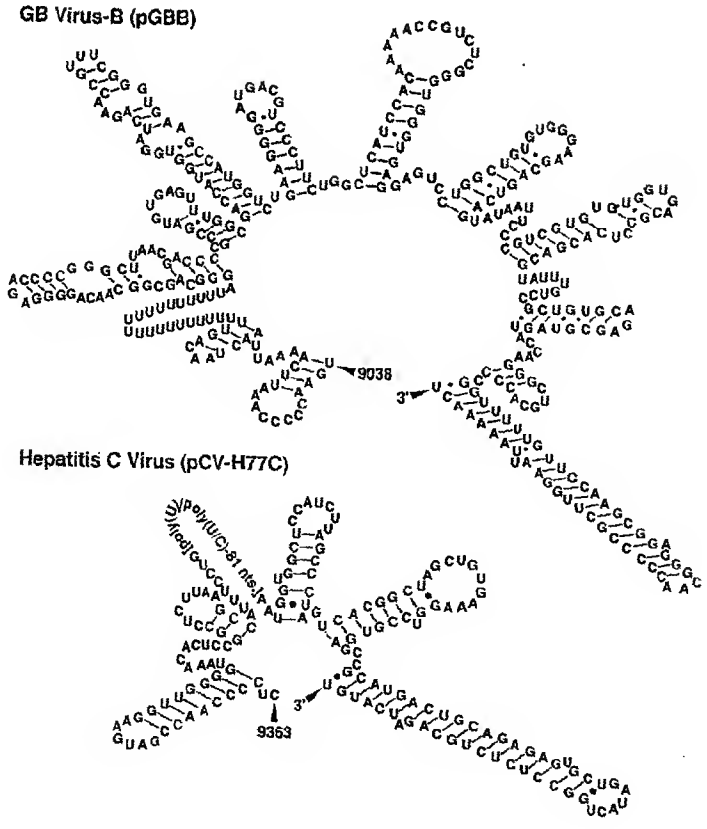
(71) Applicant *(for all designated States except US)*: **THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Offices of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BUKH, Jens** [DK/US]; 2018 Baltimore Road, #J42, Rockville, MD 20851 (US). **YANAGI, Masayuki** [JP/US]; 257 Congressional Lane, # 402, Rockville, MD 20852 (US). **EMERSON, Suzanne, U.** [US/US]; 4517 Everett Street, Kensington, MD 20895 (US). **PURCELL, Robert, H.** [US/US]; 17517 White Ground Road, Boyds, MD 20841 (US).

[Continued on next page]

(54) Title: INFECTIOUS cDNA CLONE OF GB VIRUS B AND USES THEREOF



(57) Abstract: The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B clone. The invention also relates to the use of the nucleic acid sequence of the infectious GB virus B clone to indirectly study the molecular properties of HCV, and in the production of HCV/GBV-B chimeras. The invention further relates to the use of the infectious nucleic acid sequence of GB virus B clone and the HCV/GBV-B chimeras in the development of vaccines and therapcutics for HCV.

WO 00/75337 A1

(74) **Agents: FEILER, William, S.** et al.; Morgan & Finnegan, LLP, 345 Park Avenue, New York, NY 10154 (US).

(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Title of Invention

Infectious cDNA clone of GB Virus B and Uses Thereof

Field of Invention

The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B (GBV-B) clone. The invention also relates to the use of the nucleic acid sequence of the infectious GB virus B clone to study indirectly the molecular properties of hepatitis C virus (HCV), and in the production of HCV/GBV-B chimeras. The invention further relates to the use of the infectious nucleic acid sequence of the GB virus B clone and the HCV/GBV-B chimeras in the development of vaccines and therapeutics for HCV.

Background of Invention

Transmission studies of potential human hepatitis agents were first reported in 1967 (Deinhardt 1967). Four tamarins inoculated with acute phase sera from a surgeon with acute hepatitis (patient GB) developed hepatitis, as did most tamarins inoculated in serial passage studies. Subsequent studies indicated that the etiological agent responsible for the development of hepatitis in these animals was not any of the known human hepatitis viruses (Purcell 1994). In 1995, two related RNA viruses named GB virus-B (GBV-B) and GB virus A (GBV-A) were identified in acute phase sera of a tamarin which developed hepatitis following inoculation with serum of the eleventh tamarin passage of the putative GB agent (Simons 1995a).

GBV-B infection of tamarins resulted in acute resolving hepatitis (Schlauder 1995, Buhk 1997). The

natural host of GBV-B is still unknown as the virus has not been detected in uninoculated animals or in humans.

GBV-A, on the other hand, is an indigenous tamarin virus rather than a component of the original GB inoculum (Bukh 1997, Erker 1998). Experimental infection of tamarins with GBV-A did not produce hepatitis (Schlauder 1995). A human agent, GBV-C or hepatitis G virus, most closely related to GBV-A, was later identified (Simons 1995b, Linnen 1996). However, it is still not clear whether this virus actually causes hepatitis (Alter 1998, Bukh 1998a). Thus, of the known GB viruses, GBV-B may be the only true hepatitis virus.

Based on analysis of their genomic sequences, GBV-A, GBV-B and GBV-C were classified as members of the *Flaviviridae* family of viruses, and among the known viruses, GBV-B is the virus most closely related to hepatitis C virus (HCV) (Muerhoff 1995, Robertson 1998).

The GBV-B virus contains a positive-sense, single-stranded RNA genome of 9143 nucleotides (nts) (Simons 1995a, Muerhoff 1995). The viral genome of GBV-B consists of a 5′ untranslated region (UTR), a single long open reading frame (ORF) and a 3′ UTR. Based on known motifs, structural proteins were predicted to be encoded in the 5' portion of the ORF and nonstructural (NS) proteins in the 3' portion of the ORF (Muerhoff 1995). The hydropathy plots of the polyproteins of GBV-B and HCV are very similar even though the overall homology of the predicted polyproteins between GBV-B and HCV is only about 25-30% (Muerhoff 1995). The putative envelope proteins (E1 and E2) of GBV-B and HCV share common structural features, and significant homology was observed between the NS3 serine protease, the NS3 RNA

helicase, and the NS5 RNA-dependent RNA polymerase regions of GBV-B and HCV (Muerhoff 1995). Furthermore, the function and substrate specificity of the GBV-B and HCV NS3 serine proteases are also similar (Scarselli 1997). The genomic structure and organization of GBV-B and HCV share additional features of interest. First, colinear regions with significant sequence homology were identified in the 5' UTRs (Muerhoff 1995) and the predicted IRES structure of GBV-B is similar to that of HCV (Lemon 1997). Second, both viruses begin the 3' UTR with a short sequence followed by a poly (U) stretch followed by additional nucleotides (50 nucleotides for GBV-B and 98 nucleotides for HCV). However, the 3' terminal sequence of HCV forms a stable stem-loop structure (Kolykhalov 1996) whereas the published 3' terminal sequence of GBV-B does not.

To date, molecular studies of HCV are severely limited by the lack of an efficient cell culture system for the virus and by expense and limited availability of chimpanzees, the sole animal model for HCV. Accordingly, a less expensive and more readily available animal than chimpanzees is necessary as an animal model for the study of HCV.

Summary of Invention

The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B (GBV-B) clone. It is therefore an object of the invention to provide nucleic acid sequence which encodes an infectious GBV-B. Such nucleic acid sequence is referred to throughout the application as "infectious nucleic acid sequence".

As significant structural homology exists between the genomes of GBV-B and HCV, the invention also relates to the use of infection of tamarins with the infectious nucleic acid sequence of GBV-B or with mutants of the infectious sequence to study indirectly the molecular properties of hepatitis C virus (HCV) or as a preliminary screen to identify agents which have antiviral activity against HCV.

The invention further relates to "chimeric nucleic acid sequences" consisting of portions of the infectious nucleic acid sequence of GBV-B and portions of the nucleic acid sequences of other viruses closely related to GBV-B such as HCV, GBV-C or other members of the *Flaviviridae* family which do not replicate in tamarins. In a preferred embodiment, the chimeric nucleic acid sequences consist of portions of the infectious nucleic acid sequence of GBV-B and portions of the nucleic acid sequence of HCV. The nucleic acid sequences taken from GBV-B and HCV can be open-reading frame sequences, and/or sequences from the 5'UTR and/or 3'UTR.

In one embodiment, GBV-B/HCV chimeras may be made in which 5' or 3' UTR sequences of the GBV-B infectious clone are replaced with the corresponding sequence from an HCV clone.

In another embodiment, GBV-B/HCV chimeras may be constructed in which the structural or non-structural regions of GBV-B are replaced by corresponding regions of HCV. Thus, such a chimera would contain, for example, the HCV structual region in a GBV-B "genomic backbone". Of course, it is understood by one of skill in the art that the construction of the above-described

chimeric nucleic acid sequences may be reversed such that, for example, the GBV structural region may replace the structual region of an HCV genome to produce a chimera in which the GBV structural region is contained in an HCV backbone.

The invention further relates to the use of the chimeric nucleic acid sequences of the invention to study the functions of HCV genes, and for the development of vaccine and antiviral agents against HCV.

The invention also relates to the use of the infectious GBV-B nucleic acid sequence, the mutated GBV-B nucleic acid sequences or the chimeric sequences of the invention to identify cell lines capable of supporting the replication of GBV-B or the chimeras of the invention.

The present invention also relates to the polypeptides encoded by the nucleic acid sequences of the invention or fragments thereof.

The present invention further relates to the in vitro and in vivo production of GBV-B, mutant GBV-B viruses or chimeric GBV-B/HCV viruses from the nucleic acid sequences of the invention.

The invention also provides that the nucleic acid sequences and viruses of the invention be supplied in the form of a kit, alone or in the form of a pharmaceutical composition.

Brief Description Of Figures

Figure 1 shows a flow diagram of GB virus transmission studies in two species of tamarins, *Saguinus mystax* (SM) and *Saguinus oedipus* (SO). The animals infected with GBV-B (Simons 1995a) are boxed.

Two serum pools (GB 8/93 and GB 2/94) were made from acutely infected animals. Both pools contained GBV-B, as well as GBV-A (Simons 1995) at a titer of 10^8 genome equivalent (GE)/ml. A 10% liver homogenate (CT 11/91) was made from a sacrificed tamarin. A number of *S. mystax* tamarins (SM 737, 749, 750, 760, 782, 795 and 799) and *S. oedipus* tamarins (SO 100) were naturally infected with GBV-A_{SM} and GBV-A_{SO}, respectively, prior to inoculation (Bukh 1997). Only two tamarins (SM 720 and 748), both GBV-A_{SM} negative, became infected with GBV-A (Simons 1995) following inoculation. Tamarins SM42 and SM670 were not tested for GBV-A or GBV-A_{SM}.

Figure 2 shows the course of GBV-B infection in tamarins (*S. mystax*) inoculated with a dilution series of the GB 2/94 pool. All animals were inoculated intravenously at week 0 with 1 ml of the indicated dilution. Results of qualitative RT-nested PCR for GBV-B in serum are shown at the top (filled circles, positive; empty circles, negative). Serum levels of isocitrate dehydrogenase (ICD in units/ml; shaded area) and the estimated $\log_{10}$ GBV-B GE titer (vertical columns) were plotted against time.

Figure 3 shows alignment of the 3' UTR sequences of GBV-B. The sequence of the infectious clone of GBV-B (pGBB) is shown at the top (nts. 9038-9399). The other sequences shown are: pGBB5-1, a non-infectious clone of GBV-B; GBV-B, a prototype of GBV-B (Simons 1995); eleven "gb" clones obtained from CT 11/91 liver homogenate by 5' RACE on the minus-strand GBV-B RNA; four "29" clones obtained from GB 2/94 pool by RT-PCR across 5'-to-3'-end-ligated viral GBV-B RNA; and seven "GBB3" clones obtained from GB 2/94 pool by standard RT-PCR.

With pGBB as the reference, nucleotide substitutions or insertions are shown as uppercase letters, identical nucleotides are shown as dots and nucleotide deletions are shown as dashes.

Figure 4 shows the predicted secondary structure of the 3' UTRs of GBV-B and HCV as determined by the program "mfold" (Genetics Computer Group).

Figure 5 shows the course of GBV-B infection in *S. mystax* tamarins transfected with RNA transcripts of pGBB. Both animals were negative for GBV-A_{SM}. At week 0 transcription mixtures were injected into tamarins by percutaneous intrahepatic injection guided by ultrasound. Results of qualitative RT-nested PCR for GBV-B in serum is shown at the top (filled circles, positive; empty circles, negative). Serum levels of isocitrate dehydrogenase (ICD in units/ml; shaded area) and the estimated $\log_{10}$ GBV-B GE titer (vertical columns) were plotted against time.

Figures 6A-6F show the nucleotide sequence of the infectious hepatitis C virus clone of genotype 1a strain H77C and Figures 6G-6H show the amino acid sequence encoded by the clone.

Figures 7A-7F show the nucleotide sequence of the infectious hepatitis C virus clone of genotype 1b strain HC-J4 and Figures 7G-H show the amino acid sequence encoded by the clone.

Description of The Invention

The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B (GBV-B) clone. The nucleic acid sequence which comprises the genome of an infectious GBV-B virus is

shown in SEQ ID NO:1 and is contained in the plasmid construct pGBB deposited with the American Type Culture Collection (ATCC) on May 28, 1999 and having ATCC accession number PTA-152. The present invention relates to the identification of a 260 nucleotide sequence at the 3' end of the infectious GBV-B clone which is shown in Example 3 to be necessary for the development of the infectious clone.

Since GBV-B is the virus most closely related to HCV, the present invention also relates to experimental infection of tamarins with the infectious GBV-B clone of the invention or with mutants of the infectious GBV clone to study indirectly the molecular properties of HCV or as a preliminary screen to identify agents which have antiviral activity against HCV. For example, since the predicted internal ribosome entry site (IRES) structure in the 5'UTR of GBV-B is similar to that of HCV (Lemon 1997), the NS3 serine proteases of GBV-B and HCV have been shown to share substrate specificity in vitro (Scarselli 1997), and the 3'UTRs of HCV (Yanagi 1999) and GBV-B (see Examples) have been shown to be critical for viral infectivity, mutagenesis of these regions in the GBV-B infectious clone may be undertaken to examine IRES function, NS3 serine protease activity or the role of the 3'UTR in viral infectivity in vivo. Where such "mutations" are introduced into the GBV-B clone of the invention to create a "mutated" GBV-B sequence, the mutations include, but are not limited to, point mutations, deletions and insertions. Of course, one of ordinary skill in the art would recognize that the size of the insertions would be limited by the ability of the resultant nucleic acid sequence to be

properly packaged within the virion. Such mutations could be produced by techniques known to those of skill in the art such as site-directed mutagenesis, fusion PCR, and restriction digestion followed by religation.

Alternatively, given the significant structural homology that exists between the genomes of GBV and HCV, the infectious GBV-B clone may be used to screen for inhibitors of IRES function or viral enzyme activity (for example, NS3 helicase, NS3 protease, NS2-NS3 protease or NS5B RNA polymerase activity). Such inhibitors may be useful as antiviral agents to HCV since viral enzyme activity and IRES function are known to be critical for HCV replication.

The effect of such inhibitors on the IRES function or viral activity of the GBV-B encoded by the infectious sequence of the invention may be measured by assays known to those of skill in the art to measure directly or indirectly viral replication or viral pathogenicity. Such assays include, but are not limited to, the measurement of virus titer in serum or liver of an infected tamarin by PCR or the measurement of GBV-B viral protein expression in liver cells of an infected tamarin by immunoflourescence or Western blot. Of course, it is understood that a comparison of results obtained for control tamarins (treated only with infectious nucleic acid sequence) with those obtained for treated tamarins (nucleic acid sequence and antiviral agent) would indicate, the degree, if any, of antiviral activity of the candidate antiviral agent. Of course, one of ordinary skill in the art would readily understand that the tamarins can be treated with the candidate antiviral agent either before or after

exposure to the infectious nucleic acid sequence of the present invention.

In yet another embodiment, the invention relates to "chimeric nucleic acid sequences" which consist of portions of the infectious nucleic acid sequence of GBV-B and portions of nucleic acid sequences of viruses which are related to GBV-B such as HCV, GBV-C and other members of the Flaviviridae family which do not infect tamarins. In a preferred embodiment, chimeric nucleic acid sequences consist of portions of the infectious nucleic acid sequence of GBV-B and portions of nucleic acid sequences of hepatitis C viruses (HCV) of various genotypes or subtypes; preferably portions of nucleic acid sequence of infectious HCV clones of genotypes 1a (ATCC accession number PTA-157; Figures 6A-6F), 1b (ATCC accession number 209596; Figures 7A-7F) or 2a (ATCC accession number PTA-153; SEQ ID NO: 4). The nucleic acid sequences taken from GBV-B and HCV can be open-reading frame sequences, and/or sequences from the 5'UTR and/or 3'UTR. The gene borders of the HCV genome, including nucleotide and amino acid locations, have been determined, for example, as depicted in Houghton, M. (1996), and the putative gene borders of the GBV-B are shown in Table 1.

Of course, it is understood that the production of GBV-B/HCV chimeras could include insertion of specific genes or regions of the infectious GBV-B clone into an HCV "genomic backbone" (where the HCV genomic backbone is preferably an infectious nucleic acid sequence of HCV genotypes 1a, 1b or 2a described above) or alternatively, could include insertion of

specific genes (or portions thereof) or regions of an HCV genome into the GBV-B infectious clone of the invention. Of course, where HCV genes or regions are to be inserted into the GBV-B infectious clone, it is to be understood that the inserted HCV sequences may be unmodified or may be mutated in order to examine the effect of the mutation(s) on the function of the inserted HCV gene or region in the chimeric GBV-B-HCV virus.

Such chimeras can readily be produced by methods known to those of ordinary skill in the art.

In one embodiment, GBV-B/HCV chimeras may be made in which 5' or 3' UTR sequences of the GBV-B infectious clone are replaced with the corresponding sequence from an HCV clone. For example, chimeras may be constructed in which the IRES sequence of the infectious GBV-B clone is replaced by the IRES sequence of HCV. Such chimeras can be used in identifying inhibitors of IRES activity which would be useful as antiviral agents, or could be used to examine HCV IRES function in vivo. Alternatively, mutations could be introduced into the HCV IRES contained in the GBV-B clone in order to examine the effect of the mutation(s) on IRES function in vivo.

Alternatively, GBV-B/HCV chimeras may be made in which the 3'UTR sequence of GBV-B is replaced by the 3'UTR sequence of HCV. As the 3' terminal stem-loop structure is believed to be important for initiation of RNA replication and has been shown to be critical for infectivity of HCV in vivo, such chimeras may be used for more detailed analysis of the function of the 3' UTR

sequence of HCV in vivo and for the testing of candidate antiviral agents.

In another embodiment, GBV-B/HCV chimeras may be constructed in which the structural or non-structural regions of GBV-B are replaced by corresponding regions of HCV. Such chimeras would be useful in identifying whether the inability of HCV to infect tamarins is due to the inability of HCV's structural region to bind the receptor necessary for infection of tamarins or to the absence of sequences in HCV's nonstructural regions which are necessary for replication in tamarins. For example, the ability to infect tamarins with GBV-B/HCV chimeras in which the non-structural region of GBV-B is replaced by the non-structural region of HCV would indicate that the structural genes of GBV-B are necessary for viral infection in tamarins, and that the inability of HCV to infect tamarins is likely due to its lack of receptors for HCV.

Alternatively, the ability to infect tamarins with GBV-B/HCV chimeras in which the structural region of GBV-B is replaced by the structural region of HCV would indicate that the non-structural genes of GBV-B are critical for viral infection in tamarins, and that the inability of HCV to infect tamarins is likely due to HCV's lack of nonstructural sequences which are necessary for replication in tamarins.

Of course, GBV-B-HCV chimeras may be constructed in which only a portion of the non-structural or structural regions of GBV-B are replaced by the corresponding portions of HCV sequences. For example, a chimera in which only one or two of the three structural genes (C, E1 and E2) of GBV-B are replaced by

the corresponding HCV structural genes may be made. In one embodiment, nucleic acid sequences comprising the E1 and E2 genes of GBV-B may be replaced by the sequences comprising the HCV E1 and E2 genes. In another embodiment, nucleic acid sequence comprising either the E1 or E2 gene of GBV-B is replaced by sequence encoding either the HCV E1 or E2 gene.

Alternatively, only a fragment of a GBV-B structural gene in the infectious GBV clone may be replaced with the corresponding HCV gene fragments. For example, the amino terminal of the GBV-B E1 gene may be replaced by the corresponding portion of an HCV E1 gene or an amino terminal portion of the GBV-B E2 gene may be replaced by an amino terminal portion of HCV E2 gene tht containing the HVR1 region. As the structural genes of HCV are believed to be important for neutralization, chimeras containing an HCV structural gene(s) or fragment(s) thereof can be used to develop vaccines against HCV.

In yet another embodiment, chimeras in which individual non-structural genes of GBV-B, such as NS3 RNA helicase, NS3 protease, or the NS5B RNA-dependent RNA polymerase are replaced by the corresponding non-structural genes of HCV may be constructed. Such chimeras would, for example, be useful in identifying inhibitors of viral enzyme activity which would be useful as antiviral agents. Of course, it is understood that in order to construct chimeras in which the polyprotein cleavage sites of the GBV-B remain intact, it may be desirable to replace only a fragment of a nonstructural gene of GBV-B with the corresponding HCV gene fragment.

The present invention also relates to polypeptides encoded by the nucleic acid sequences of the invention or fragments thereof. In one embodiment, said polypeptide or polypeptides may be fully or partially purified from viruses produced by cells transfected with the nucleic acid sequences of the invention. In another embodiment, the polypeptide or polypeptides may be produced recombinantly from a fragment of the nucleic acid sequences of the invention. In yet another embodiment, the polypeptides may be chemically synthesized.

The present invention further relates to the in vitro and in vivo production of GBV-B, mutated GBV-B or chimeric GBV-B/HCV viruses from the nucleic acid sequences of the invention.

In one embodiment, the sequences of the invention can be inserted into an expression vector that functions in eukaryotic cells. Eukaryotic expression vectors suitable for producing high efficiency gene transfer in vivo are well known to those of ordinary skill in the art and include, but are not limited to, plasmids, vaccinia viruses, retroviruses, adenoviruses and adeno-associated viruses.

In another embodiment, the sequences contained in the recombinant expression vector can be transcribed in vitro by methods known to those of ordinary skill in the art in order to produce RNA transcripts which encode the GBV-B of the invention. The GBV-B of the invention may then be produced by transfecting cells by methods known to those of ordinary skill in the art with either the in vitro transcription mixture containing the RNA

transcripts or with the recombinant expression vectors containing the nucleic acid sequences described herein.

In assaying the ability of the mutated GBV-B sequences or of the chimeric sequences of the invention to infect tamarins, the virulence phenotype of the virus produced by transfection of tamarins with the sequences of the invention can be monitored by methods known in the art such as measurement of liver enzyme levels (alanine aminotransferase (ALT) or isocitrate dehydrogenase (ICD)) or by histopathology of liver biopsies.

The present invention also relates to the use of the infectious GBV-B sequence, the mutated GBV-B nucleic acid sequences or the chimeric sequences of the invention to identify cell lines capable of supporting the replication of GBV-B or the chimeras of the invention.

Transfection of tissue culture cells with the nucleic acid sequences of the invention may be done by methods of transfection known in the art such as electroporation, precipitation with DEAE-Dextran or calcium phosphate, or incorporation into liposomes.

In one such embodiment, the method comprises the growing of animal cells in vitro and transfecting the cells with the nucleic acid of the invention, then determining if the cells show indicia of GBV-B or HCV infection. Such indicia include the detection of viral antigens in the cell, for example, by immunofluorescence procedures well known in the art; the detection of viral polypeptides by Western blotting using antibodies specific therefor; and the detection of newly transcribed viral RNA within the cells via methods such

as RT-PCR. The presence of live, infectious virus particles following such tests may also be shown by injection of cell culture medium or cell lysates into healthy, susceptible animals, with subsequent exhibition of the signs and symptoms of GBV-B infection.

Suitable cells or cell lines for culturing GBV-B or the chimeric GBV-B-HCV include, but are not limited to, lymphocyte and hepatocyte cell lines known in the art.

Alternatively, primary hepatocytes can be cultured, and then infected; or, the hepatocyte cultures could be derived from the livers of infected tamarins. In addition, various immortalization methods known to those of ordinary skill in the art can be used to obtain cell-lines derived from hepatocyte cultures. For example, primary hepatocyte cultures may be fused to a variety of cells to maintain stability.

The invention also provides that the nucleic acid sequences and viruses of the invention be supplied in the form of a kit, alone or in the form of a pharmaceutical composition.

All scientific publication and/or patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

Materials and Methods

Source of GB virus B

Two tamarin pools VR-806, (American Type Culture Collection) and H205, were used for experimental

transmission of the GB virus agents to tamarins species *Saguinus mystax* and *Saguinus oedipus*.

Amplification, cloning and sequence analysis of GBV-B

Viral RNA was extracted from aliquots of the GB 2/94 serum pool or CT 11/91 liver homogenate with the TRIzol system (GIBCO/BRL). Primers used in cDNA synthesis and PCR amplification were based on the genomic sequence of GBV-B published by Simons et al (Simons 1995) shown in SEQ ID NO:3. Long RT-PCR was performed using Superscript II reverse transcriptase (GIBCO/BRL) and the Advantage cDNA polymerase mix (Clontech) as described previously (Tellier 1996). Four subgenomic regions of GBV-B covering the entire published sequence (Simons 1995) were amplified from serum and the PCR products were purified and cloned into pGEM-9Zf(-) (Promega) or pCR2.1 vector (Invitrogen) using standard procedures.

The 5' terminus of GBV-B was amplified from serum by using the rapid amplification of cDNA ends (RACE) with dC or dA tailing (GIBCO/BRL) and GBV-B specific antisense primers. Two different approaches were used to determine the 3' terminal sequence of GBV-B. In one approach, GBV-B RNA extracted from serum was circularized with T4 RNA ligase (Promega) and the 5'-to-3'-end-ligated viral RNA was amplified in RT-PCR using specific GBV-B primers. In the second approach, the 5' end of the negative strand GBV-B RNA extracted from the liver homogenate was amplified using the 5' RACE with dC tailing and GBV-B specific sense primers. The PCR products were cloned directly into pCR2.1-TOPO by using the TOPO TA Cloning Kit (Invitrogen).

The consensus sequence of GBV-B was determined by direct sequencing of PCR products (nucleotides 1-9078 and nucleotides 9130-9359) and by sequence analysis of the clones (nucleotides 1-7135 and nucleotides 7151-9399). Nucleotide positions correspond to those of the infectious clone (pGBB). Analyses of genomic sequences were performed with GeneWorks (Oxford Molecular Group) (Bukh 1995). To determine whether the GenBank data base contained sequences with homology to the GBV-B 3' UTR sequence identified in the present invention, a "Blast" search was performed. The predicted secondary structure of the GBV-B and HCV 3' UTR sequences were determined by the program "mfold" (Genetics Computer Group).

Construction of consensus cDNA clones of GBV-B

First, clone pGBB5-1, a consensus clone of GBV-B 2/94 containing the 3' terminus of GBV-B as published by Simons *et al* was constructed (Simons 1995a). The core sequence of the T7 promoter, a 5' guanosine residue and the sequence of GBV-B (9139 nucleotides) were cloned into pGEM-9Zf(-) vector using *Not*I/*Sac*I sites. A *BamH*I site was included at the GBV-B 3' terminus. Digested fragments containing the consensus sequence were purified from subclones and ligated using convenient sites. Next, a second consensus clone of GBV-B, clone pGBB, was constructed by inserting the additional 3' terminal sequence, amplified by PCR from one of the clones obtained by the RACE procedure described above, into pGBB5-1 using *Xma*I (at position 9114) and *BamH*I sites. A *Xho*I site was inserted following the GBV-B 3' terminus. DH5-alpha competent cells (GIBCO BRL) were transformed and selected on LB agar plates containing 100 µg/ml

ampicillin (SIGMA) and amplified in LB liquid cultures at 30°C for 18-20 hrs (Yanagi 1997). Each cDNA clone was re-transformed to select a single clone, and large-scale preparation of plasmid DNA was performed with a QIAGEN plasmid Maxi kit as described previously (Yanagi 1997). Each clone was genetically stable since the digestion pattern was as expected following retransformation and the complete sequence was the expected one.

Intrahepatic transfection of tamarins with transcribed GBV-B RNA

In 100 µl reactions, RNA was transcribed *in vitro* with T7 RNA polymerase (Promega) from 10 µg of linearized template plasmid. The plasmid pGBB5-1 was linearized with *BamH*I (Promega) and the plasmid pGBB was linearized with *Xho*I (Promega). The integrity of the RNA was checked by electrophoresis through agarose gel stained with ethidium bromide. Each transcription mixture was diluted with 400 µl of ice-cold phosphate-buffered saline without calcium or magnesium (SIGMA) and then immediately frozen on dry ice and stored at -80°C. Within 24 hours of synthesis, two transcription mixtures were injected into each tamarin by percutaneous intrahepatic injection guided by ultrasound (Emerson, 1992; Yanagi 1998, 1999). If the tamarin did not become infected, the same transfection was repeated once. All transfected animals were negative for GBV-A_{SM} as determined by the protocol described previously (Bukh 1997a).

Monitoring of experimental course in tamarins

Serum samples were collected weekly from the tamarins and monitored for liver enzyme levels [alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), and isocitrate dehydrogenase (ICD)] by standard methods and for GBV-B RNA by a specific reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Total RNA was extracted from 100 µl of serum using the TRIzol reagent. The RNA pellet was resuspended in 10 mM dithiothreitol (DTT) containing 5% (vol/vol) of RNasin (20-40 u/µl) (Promega). The RT-nested PCR was performed with primers from the 5' UTR of GBV-B (external primer pair: 5'-CCT AGC AGG GCG TGG GGG ATT TCC-3' and 5'-AGG TCT GCG TCC TTG GTA GTG ACC-3'; internal primer pair: 5'-GGA TTT CCC CTG CCC GTC TG-3' and 5'-CCC CGG TCT TCC CTA CAG TG-3'). The reverse transcription was performed with avian myeloblastosis virus reverse transcriptase (Promega) and the external anti-sense primer and nested PCR was performed with AmpliTaq DNA polymerase or AmpliTaq Gold DNA polymerase (Perkin Elmer) as described previously (Bukh 1998a). Specificity was confirmed by sequence analysis of selected DNA products. Each set of experiments included a positive control sample (a 10^{-6} dilution of GB 8/93, estimated titer 100 genome equivalent (GE)) and appropriate negative control samples. The genome equivalent (GE) titer of GBV-B in positive samples was determined by RT-nested PCR on 10-fold serial dilutions of the extracted RNA (Bukh 1998a). One GE was defined as the number of GBV-B genomes present in the highest dilution positive in RT-nested PCR. The sensitivity of this RT-nested PCR assay for GBV-B was equivalent to that of our RT-nested PCR assay for HCV (Bukh 1998b), for example, conserved NS3

primers which had the same sensitivity for GBV-B as the 5' UTR primers could detect HCV at optimal sensitivity in samples with known HCV genome titer. Testing for GBV-A and GBV-A variants was performed by RT-nested PCR assays as described previously (Bukh 1997a).

The consensus sequence of the complete ORF was determined by direct sequencing of overlapping PCR products obtained by long RT-nested PCR on serum from one of the tamarins infected with RNA transcripts as previously described (Yanagi 1997).

Example 1

Transmission of GB Agent in Tamarins

To generate virus pools of the GB agent, tamarins were inoculated intravenously with pooled sera of the eleventh tamarin passage of this agent (Fig. 1). Acute phase sera from a *S. mystax* tamarin which developed hepatitis were pooled (GB 8/93) and inoculated into additional *S. mystax* tamarins to generate a second pool of acute phase serum (GB 2/94). Both serum pools contained approximately 10^8 GE/ml of GBV-B and GBV-A. A 10% liver homogenate (CT 11/91) was prepared from a *S. oedipus* tamarin which developed hepatitis following inoculation with the twelfth passage of the GB agent. The titer of GBV-B in the liver homogenate was approximately 10^7 GE/ml. The GB 2/94 serum and CT 11/91 liver samples were used as GBV-B cloning sources in the present study.

Inoculation of eight *S. mystax* tamarins with ten-fold serial dilutions of the GB 2/94 pool demonstrated that its infectivity titer of GBV-B was 10^8 tamarin 50% infectious doses (TID_{50}) (Fig. 2). The five

GBV-B infected tamarins all developed acute resolving hepatitis characterized by early appearance of viremia (weeks 1 or 2 p.i.), peak viral titers of 10^7-10^8 GE/ml and clearance of viremia after 9-16 weeks (Fig. 2). Two of these tamarins (*S. mystax* 769 and 777) were infected only with GBV-B and were negative for GBV-A and GBV-A_{SM}, whereas the other three tamarins were infected with both GBV-B and GBV-A_{SM}. A *S. mystax* tamarin inoculated with the liver homogenate also developed acute resolving hepatitis with peak GBV-B titers of 10^7 GE/ml and clearance of viremia after 11 weeks. Likewise, four *S. mystax* tamarins inoculated with dilutions of the GB 8/93 pool developed acute resolving hepatitis with clearance of the GBV-B virus after 11-26 weeks. Thus, GBV-B infection in *S. mystax* tamarins is characterized by acute hepatitis, early appearance of viremia, high peak viral titers and viral clearance.

Example 2

Novel 3' Terminal Sequence of GBV-B

The consensus sequence of the complete 5' UTR of GBV-B (nucleotides 1-445) was deduced from 13 clones containing nucleotides 1-283 and 3 clones containing nucleotides 31-445. In addition, the entire 5' UTR sequence was determined by direct sequencing of the amplicons. The sequences of the various clones were highly conserved and the consensus 5' UTR sequence of GBV-B from this pool was identical to that of the previously published sequence for GBV-B (Simons 1995a). It is noteworthy that 13 of 15 clones analyzed from the rapid amplification of cDNA ends (RACE) procedure contained the published GBV-B 5' terminus (A residue)

and that the same 5' terminus was obtained whether the 5' RACE was performed with dC or dA tailing.

The consensus sequence of the ORF (nucleotides 446-9037) was determined by direct sequencing of PCR products obtained using long RT-PCR (Yanagi 1997). In addition, 3 clones containing nts. 446-7135 (one of these clones had a deletion of nts. 3036-3636), 2 clones containing nts. 2019-3373, 5 clones containing nts. 7151-8261 and 7 clones containing nts. 7521-9037 were analyzed. The sequences of GBV-B clones in this pool were very homogeneous. Evidence of micro-heterogeneity was found at only 70 (0.8%) nucleotide and 36 (1.3%) amino acid positions, scattered throughout the ORF. The proportion of amino acid positions with heterogeneity ranged from 0.5-3.2% in different putative gene regions (lowest in NS3 and NS5B; highest in E2 and NS2). The GBV-B ORF sequence differed from the published sequence of GBV-B (Simons 1995) at 34 (0.4%) nucleotide and 12 (0.4%) deduced amino acid positions, respectively (Table 1).

Table 1

Nucleotide and amino acid differences among GBV-B (Simons 1995a), the consensus sequence of GBV-B recovered from a virus pool used as the cloning source (GBV-B, 2/94) and the infectious clone of GBV-B (pGBB).

Genomic Region*	Position nt [aa]	Nucleotide			Amino Acid		
		GBV-B	GBV-B 2/94	pGBB	GBV-B	GBV-B 2/94	PGBB
5' UTR (1-445)							
C (446-913)							
E1 (914-1489)	1030	C	T	T			
E2 (1490-2641)	1498	T	C (t)	C			
	1628 [395]	G	A (g)	A	V	I (V)	I
	2552 [703]	G	A (g)	A	D	N (D)	N
	2562,2563 [706]	C,A	A,C	A,C	P	H	H
	2566	T	T	T			
	2625 [727]	C	T	T	A	V	V
NS2 (2642-3385)	2647	C	T (c)	T			
	2816 [791]	C	T	T	L	F	F
	2855 [804]	A	G	G	T	A	A
	3235	A	G	G			
NS3 (3386-5125)	3475**	C	C (t)	T			
	3760	C	T (c)	T			
	4114	C	T	T			
	4117	C	A	A			
	4177	T	C	C			
	4615	C	T	T			
NS4A (5126-5290)							
NS4B (5291-6034)	5329	C	T	T			
	5332	T	C	C			
	5350	A	C	C			
	5455	C	T (c)	T			
NS5A (6035-7267)	6413 [1990]	T	A (t)	A	L	M (L)	M
	6577	G	T	T			
	6690 [2082]	T	C (t)	C	I	T(I)	T
	6965 [2174]	T	C (t)	C	S	P (S)	P
	7015	A	G (a)	G			
	7128 [2228]	G	A	A	G	E	E
	7138**	A	A	G			
	7142 [2233]	A	G	G	T	A	A
NS5B (7268-9037)	7282	T	C (t)	C			
	7849	C	A	A			
	7852	C	T	T			
	8942 [2981]	G	A (g)	A	V	I (V)	I
	8971	T	C	C			
	9026	C	T (c)	T			
3' UTR (9038-9399)	9067	T	C	C			
	Poly(U)	27 nts	11-23 nts	23 nts			
	9134	Deletion	C	C			
	9141-9399	ND	259 nts	259 nts			

*Nucleotide positions corresponding to pGBB. Putative gene borders defined as suggested by homology with HCV (Muerhoff 1995). No homology was observed at the NS2-NS3 junction.

**Positions that differ between the cloning source (GBV-B 2/94) and the infectious clone of GBV-B (pGBB). The change introduced into pGBB at position 7138 introduced an artificial *SalI* site. nd: Not determined. Nucleotides and amino acids shown in parenthesis were found as a minor species in the cloning source (GBV-B, 2/94

The sequence for the 3' UTR is shown in Figure 3. Additional 3' UTR sequence was initially identified by performing RT-PCR across 5'-to-3'-end-ligated viral RNA extracted from serum. In all 4 clones with GBV-B sequences, the 5' UTR was truncated compared to the published sequence (simon 1995a). However, whereas one clone (29c) had the exact 3' terminus previously published by Simons *et al.* (Simons 1995a), the three other clones (29a, 29b, 29d) had 150 additional terminal nucleotides. Compared with the published sequence, all four clones had a single nucleotide insertion (C residue) at position 9134. Next, RACE using dC-tailing only was performed on the 5' end of the negative-strand RNA extracted from the liver homogenate. All 11 clones analyzed had additional sequences at the 3' terminus. Compared with the published GBV-B sequence, two clones (gb6, gb23) had 259 additional nucleotides, 8 clones (gb9, gb19, gb20, gb21, gb24, gb25, gb30, gb35) had 236 additional nucleotides and 1 clone (gb8) had 232 additional nucleotides. Moreover, all of these clones had the insertion at position 9134. The 3' UTR sequences among the various clones were highly conserved (Fig. 3). To demonstrate that the terminal 22 nucleotides found only in clones gb6 and gb23 existed in circulating viruses, RT-nested PCR was performed on 10-fold serially diluted RNA extracted from the serum pool GB 2/94 using an RT and external antisense primer deduced from this sequence. GBV-B RNA was detected at a dilution of 10^{-7} and the sequence of the amplicon was identical to the sequence recovered from the liver homogenate. Thus, the 3' UTR of GBV-B consists of a short sequence of 30 nucleotides followed by a 11-24

nucleotide-long poly (U) tract (single C residues were observed in GBV-B from the liver homogenate) and a 3' terminal sequence of at least 309 nucleotides. The new GBV-B 3' UTR sequence did not have significant homology to any of the sequences deposited in the GenBank database. A prediction of the secondary structure of the 3' UTR sequence is shown in Figure 4. The most notable feature of the secondary structure is a highly stable stem-loop structure at the very 3' end consisting of 47 nucleotides.

Example 3

The pGBB Clone of GBV-B is Infectious *in vivo*

The infectivity of RNA transcripts from the consensus clone pGBB5-1 which encompassed only the published GBV-B sequence (Simons 1995) was first tested. Within the GBV-B sequence there were no deduced amino acid differences and only 2 nucleotide differences (at nucleotide positions 3475 and 7138) between the consensus sequence of the cloning source (GBV-B 2/94) and the sequence of pGBB5-1 clone. In addition, the 3' UTR of pGBB5-1 had a deletion at nucleotide position 9134 and was missing the 3' terminal 259 nucleotides (Fig. 3). Prior to transcription, the pGBB5-1 clone was linearized at the *BamHI* site with digestion at the exact GBV-B 3' terminus. The RNA transcripts from pGGB5-1 were injected into the liver of two tamarins (*S. mystax* 797 and 815). GBV-B RNA was not detected in weekly serum samples collected during 17 weeks of follow-up. As the susceptibility of these two tamarins to GBV-B was subsequently demonstrated by experimental infection using a GBV-B virus pool, the consensus clone pGBB5-1

which lacks the 3' terminal sequence of GBV-B is thus not infectious *in vivo*.

Next, the infectivity of RNA transcripts from the full-length consensus GBV-B cDNA clone pGBB was tested. The pGBB clone was identical to the pGBB5-1 clone except in the 3' UTR. Thus, in addition to a 5' UTR of 445 nucleotides, an ORF of 8592 nucleotides encoding 2864 amino acids and a 3' UTR of 103 nucleotides, the pGBB clone also contains an additional 259 nucleotides in its 3' UTR. pGBB was linearized at the *Xho*I site which added an additional C residue at the 3' end of the transcribed GBV-B RNA. When RNA transcripts from the pGBB clone were injected into the liver of two tamarins (*S. mystax* 816 and 817), both tamarins became infected with GBV-B with viremia at week 1 p.i. and peak viral titers of 10^8 GE/ml (Fig. 5). The consensus sequence of PCR products of the complete ORF, amplified from serum obtained during week 2 p.i. from one tamarin (*S. mystax* 817), was identical to the sequence of pGBB, including at the two positions which differed from the consensus sequence of the cloning source and from the published sequence of GBV-B (Table 1). By performing RT-PCR as desired above, it was demonstrated that the very 3' terminal GBV-B sequence of pGBB existed in the circulating viruses in this tamarin. Within two weeks of the transfection both tamarins developed hepatitis with dramatically elevated liver enzyme levels (Fig. 5). Thus, the pGBB clone is infectious *in vivo* whereas the clone pGBB5-1 which lacks the last 259 nucleotides was not.

References

1. Alter, H. J., Nakatsuji, Y., Melpolder, J., Wages, J., Wesley, R., Shih, J. W.-K. & Kim, J. P. (1997) The incidence of transfusion-associated hepatitis G virus infection and its relation to liver disease. *N. Engl. J. Med.* 336, 747-754.

2. Alter, M. J., Gallagher, M., Morris, T. T., Moyer, L. A., Meeks, E. L., Krawczynski, K., Kim, J. P. & Margolis, H. S. (1997) Acute non-A-E hepatitis in the United States and the role of hepatitis G virus infection. *N. Engl. J. Med.* 336, 741-746.

3. Bukh, J. & Apgar, C. L. (1997a) Five new or recently discovered (GBV-A) virus species are indigenous to New World monkeys and may constitute a separate genus of the *Flaviviridae*. *Virology* 229, 429-436.

4. Bukh, J., Apgar, C. L., Engle, R., Govindarajan, S., Hegerich, P. A., Tellier, R., Wong, D. C., Elkins, R. & Kew, M. C. (1998b) Experimental infection of chimpanzees with hepatitis C virus of genotype 5a: genetic analysis of the virus and generation of a standardized challenge pool. *J. Infect. Dis.* 178, 1193-1197.

5. Bukh, J., Apgar, C. L. and Purcell, R. H. (1997b) Natural history of GBV-A and GBV-B in animal models: discovery of indigenous *Flaviviridae*-like viruses in several species of New World monkeys. In *Viral Hepatitis and Liver Disease* (Proceedings of the IX Triennial International Symposium on Viral Hepatitis and Liver Disease, Rome, Italy, 1996) (M. Rizzetto, R. H. Purcell, J. L. Gerin, G. Verme, Eds.), pp. 392-395. Edizione Minerva Medica, Turin, Italy.

6. Bukh, J., Kim, J. P., Govindarajan, S., Apgar, C. L., Foung, S. K. H., Wages, J., Yun, A. J., Shapiro, M., Emerson, S. U. & Purcell, R. H. (1998a) Experimental infection of chimpanzees with hepatitis G virus and genetic analysis of the virus. *J. Infect. Dis.* 177, 855-862.

7. Bukh, J., Miller, R. H. & Purcell, R. H. (1995) Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. *Semin. Liver Dis.* 15, 41-63.

8. Deinhardt, F., Holmes, A. W., Capps, R. B. & Popper, H. (1967) Studies on the transmission of human viral hepatitis to marmoset monkeys: Transmission of disease, serial passages, and description of liver lesions. *J. Exp. Med.* 125, 673-687.

9. Emerson, S. U., , Lewis, M., Govindarajan, S., Shapiro, M., Moskal, T. & Purcell, R. H. (1992) cDNA clone of hepatitis A virus encoding a virulent virus: induction of viral hepatitis by direct nucleic acid transfection of marmosets. *J. Virol.* 66, 6649-6654.

10. Erker, J. C., Desai, S. M., Leary, T. P., Chalmers, M. L., Montes, C. C. & Mushahwar, I. K. (1998) Genomic analysis of two GB virus A variants isolated from captive monkeys. *J. Gen. Virol.* 79, 41-45.

11. Frolov, I., McBride, M. S. & Rice, C. M. (1998) Cis-acting RNA elements required for replication of bovine viral diarrhea virus-hepatits C virus 5' nontranslated region chimeras. *RNA* 4, 1418-1435.

12. Houghton, M. (1996) Hepatitis C viruses. In "Fields Virology" (B. N. Fields, D. M. Knipe, P. M. Howley, *et al.*, Eds.), Third ed., pp. 1035-1058. Lippincott-Raven Publishers, Philadelphia.

13. Kolykhalov, A. A., Feinstone, S. M. & Rice, C. M. (1996) Identification of a highly conserved sequence element at the 3' terminus of hepatitis C virus genome RNA. *J. Virol.* 70, 3363-3371.

14. Kolykhalov, A. A., Agapov, E. V., Blight, K. J., Mihalik, K., Feinstone, S. M. & Rice, C. M. (1997) Transmission of hepatitis C by intrahepatic inoculation with transcribed RNA. *Science* 277, 570-574.

15. Lemon, S. M. & Honda, M. (1997) Internal ribosome entry sites within the RNA genomes of hepatits C virus and other flaviviruses. *Semin. Virol.* 8, 274-288.

16. Linnen, J., Wages, J., Jr., Zhang-Keck, Z. Y., Fry, K. E., Krawczynski, K. Z., Alter, H., Koonin, E., Gallagher, M., Alter, M., Hadziyannis, S., Karayiannis, P., Fung, K., Nakatsuji, Y., Shih, J. W.-K., Young, L., Piatak, M., Jr., Hoover, C., Fernandez, J., Chen, S., Zou, J.-C., Morris, T., Hyams, K. C., Ismay, S., Lifson, J. D., Hess, G., Foung, S. K. H., Thomas, H., Bradley, D., Margolis, H. & Kim, J. P. (1996) Molecular cloning and disease association of hepatitis G virus: A transfusion-transmissible agent. *Science* 271, 505-508.

17. Lu, H.-H. & Wimmer, E. (1996) Poliovirus chimeras replicating under the translational control of genetic elements of hepatitis C virus reveal unusual properties of the internal ribosomal entry site of hepatitis C virus. *Proc. Natl. Acad. Sci. USA* 93, 1412-1417.

18. Muerhoff, A. S., Leary, T. P., Simons, J. N., Pilot-Matias, T. J., Dawson, G. J., Erker, J. C., Chalmers, M. L., Schlauder, G. G., Desai, S. M. & Mushahwar I. K. (1995) Genomic organization of GB viruses A and B: Two new members of the *Flaviviridae* associated with GB agent hepatitis. *J. Virol.* 69, 5621-5630.

19. Purcell RH. (1993) The discovery of the hepatitis viruses. *Gastroenterology* 104, 955-963.

20. Rice, C. M. (1996) *Flaviviridae*: The viruses and their replication, In "Fields Virology". (B. N. Fields, D. M. Knipe, P. M. Howley, et al., Eds.), Third ed., pp. 931-959. Lippincott-Raven Publishers, Philadelphia.

21. Robertson, B., Myers, G., Howard, C., Brettin, T., Bukh, J., Gaschen, B., Gojobori, T., Maertens, G., Mizokami, M., Nainan, O., Netesov, S., Nishioka, K., Shin-i, T., Simmonds, P., Smith, D., Stuyver, L. & Weiner, A. (1998). Classification, nomenclature, and database development for hepatitis C virus (HCV) and related viruses: proposals for standardization. *Arch. Virol.* 143, 2493-2503.

22. Scarcelli, E., Urbani, A., Sbardellati, A., Tomei, L., De Francesco, R. & Traboni, C. (1997) GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity. *J. Virol.* 71, 4985-4989.

23. Schlauder, G. G., Dawson, G. J., Simons, J. N., Pilot-Matias, T. J., Gutierrez, R. A., Heynen, C. A., Knigge, M. F., Kurpiewski, G. S., Buijk, S. L., Leary, T. P., Muerhoff, A. S., Desai, S. M. & Mushahwar I. K. (1995) Molecular and serologic analysis in the transmission of the GB hepatitis agents. *J. Med. Virol.* 46, 81-90.

24. Simons, J. N., Pilot-Matias, T. J., Leary, T. P., Dawson, G. J., Desai, S. M., Schlauder, G. G., Muerhoff, A. S., Erker, J. C., Buijk, S. L., Chalmers, M. L., Van Sant, C. L. & Mushahwar, I. K. (1995a) Identification of two flavivirus-like genomes in the GB hepatitis agent. *Proc. Natl. Acad. Sci. USA* 92, 3401-3405.

25. Simons, J. N., Leary, T. P., Dawson, G. J., Pilot-Matias, T. J., Muerhoff, A. S., Schlauder, G. G., Desai, S. M. & Mushahwar, I. K. (1995b) Isolation of novel virus-like sequences associated with human hepatitis. *Nature Med.* 1, 564-569.

26. Tanaka, T., Kato, N., Cho, M.-J. & Shimotohno, K. (1995) A novel sequence found at the 3' terminus of

hepatitis C virus genome. *Biochem. Biophys. Res. Commun.* 215, 744-749.

27. Tellier, R., Bukh, J., Emerson, S. U., Miller, R. H. & Purcell, R. H. (1996) Long PCR and its application to hepatitis viruses: amplification of hepatitis A, hepatitis B, and hepatitis C virus genomes. *J. Clin. Microbiol.* 34, 3085-3091.

28. Yanagi, M., Purcell, R. H., Emerson, S. U. & Bukh, J. (1997) Transcripts from a single full-length cDNA clone of hepatitis C virus are infectious when directly transfected into the liver of a chimpanzee. *Proc. Natl. Acad. Sci. USA* 94, 8738-8743.

29. Yanagi, M., St. Claire, M., Shapiro, M., Emerson, S. U., Purcell, R. H. & Bukh, J. (1998) Transcripts of a chimeric cDNA clone of hepatitis C virus genotype 1b are infectious *in vivo*. *Virology* 244, 161-172.

30. Yanagi, M., St. Claire, M., Emerson, S. U., Purcell, R. H. & Bukh, J. (1999) *In vivo* analysis of the 3' untranslated region of the hepatitis C virus after *in vitro* mutagenesis of an infectious cDNA clone. *Proc. Natl. Acad. Sci. USA* 96, 2291-2295.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule which encodes GB virus-B, said molecule capable of expressing said virus when transfected into cells.

2. The nucleic acid molecule of claim 1, wherein said molecule encodes the amino acid sequence of SEQ ID NO:2.

3. The nucleic acid molecule of claim 2, wherein said molecule comprises the nucleic acid sequence of SEQ ID NO:1.

4. A DNA construct comprising a nucleic acid molecule according to claim 1.

5. A DNA construct comprising a nucleic acid molecule according to claim 3.

6. An RNA transcript of the DNA construct of claims 4 or 5.

7. A cell transfected with the DNA construct of claims 4 or 5.

8. A cell transfected with RNA transcripts of claim 6.

9. A GB virus-B polypeptide produced by the cell of claim 7.

10. A GB virus-B polypeptide produced by the cell of claim 8.

11. A GB virus-B produced by the cell of claim 7.

12. A GB virus-B produced by the cell of claim 8.

13. A GB virus-B whose genome comprises a nucleic acid molecule according to claim 1.

14. A GB virus-B whose genome comprises a nucleic acid molecule according to claim 3.

15. A method for producing a GB virus-B comprising transfecting a host cell with the DNA construct of claims 4 or 5.

16. A method for producing a GB virus-B comprising transfecting a host cell with the RNA transcript of claim 6.

17. A composition comprising a nucleic acid molecule of claim 1 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

18. A composition comprising a nucleic acid molecule of claim 3 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

19. A nucleic acid molecule comprising a chimeric virus genome, said genome being a GB virus-B genome according to claim 1 in which a 3′ or 5′ UTR sequence of the genome is replaced by a corresponding region of the 3′ or 5′ UTR sequence of a hepatitis C virus genome.

20. The nucleic acid molecule of claim 19, wherein a 3′ UTR sequence of the genome of a GB virus-B is replaced by a corresponding 3′ UTR sequence of a hepatitis C virus genome.

21. The nucleic acid molecule of claim 20, wherein the 3′ UTR sequence is the 3′ UTR terminal stem loop sequence.

22. The nucleic acid molecule of claim 19, wherein a 5' UTR sequence of the genome of a GB virus-B has been replaced by a corresponding 5' UTR sequence of a hepatitis C virus genome.

23. The nucleic acid molecule of claim 22, wherein the 5' UTR sequence is the IRES sequence.

24. A nucleic acid molecule comprising a chimeric virus genome, said genome being a GB virus-B genome according to claim 1 in which the non-structural region of the genome of a GB virus-B has been replaced by the non-structural region of a hepatitis C virus genome.

25. The nucleic acid molecule of claim 24, wherein at least one gene from the non-structural region of the genome of a GB virus-B has been replaced by the corresponding gene from the non-structural region of a hepatitis C virus genome.

26. The nucleic acid molecule of claim 25, wherein the gene from the non-structural region is selected from the group consisting of NS3 protease, NS3 RNA helicase, or NS5B RNA polymerase.

27. A nucleic acid molecule comprising a chimeric virus genome, said genome being a GB virus-B genome according to claim 1 in which the structural region of the genome of a GB virus-B has been replaced by the structural region of a hepatitis C virus genome.

28. The nucleic acid molecule of claim 27, wherein at least one gene from the structural region of the genome of a GB virus-B has been replaced by the

corresponding gene from the structural region of a hepatitis C virus genome.

29. The nucleic acid molecule of claim 28, wherein the gene from the structural region is selected from the group consisting of E1, E2 or C.

30. The nucleic acid molecule of claim 28, wherein the E1 and E2 genes from the structural region of the genome of a GB virus-B have been replaced by the E1 and E2 genes of a hepatitis C virus genome.

31. The nucleic acid molecule of claim 28, wherein the E1 gene from the structural region of the genome of a GB virus-B has been replaced by the E1 gene of a hepatitis C virus genome.

32. The nucleic acid molecule of claim 28, wherein the E2 gene from the structural regions of the genome of a GB virus-B has been replaced by the E2 gene of a hepatitis C virus genome.

33. A DNA construct comprising the nucleic acid molecule of claims 19, 24 or 27.

34. An RNA transcript of the DNA construct of claim 33.

35. A virus whose genome comprises a nucleic acid molecule according to claims 19, 24 or 27.

36. A nucleic acid molecule comprising a chimeric virus genome, said genome being a hepatitis C virus genome in which a 3′ or 5′ UTR sequence of the genome is replaced by a corresponding region of the 3′ or 5′ UTR sequence of a GB virus-B genome according to claim 1.

37. A nucleic acid molecule comprising a chimeric virus genome, said genome being a hepatitis C virus genome in which the non-structural region of the genome has been replaced by the non-structural region of a GB virus-B genome according to claim 1.

38. A nucleic acid molecule comprising a chimeric virus genome, said genome being a hepatitis C virus genome in which the structural region of the genome has been replaced by the structural region of a GB virus-B genome according to claim 1.

39. A polypeptide encoded by the nucleic acid molecule of claims 19, 24 or 27.

40. A polypeptide encoded by the nucleic acid molecule of claims 36, 37 or 38.

FIG. 1

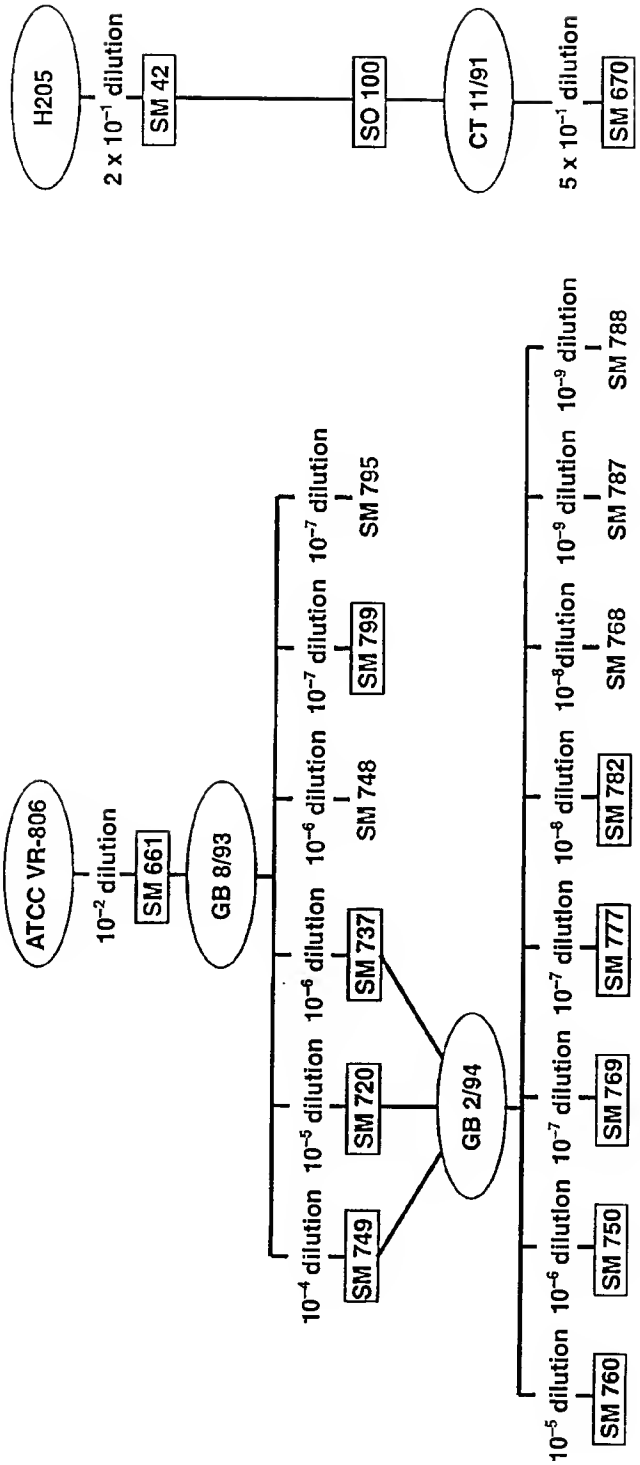
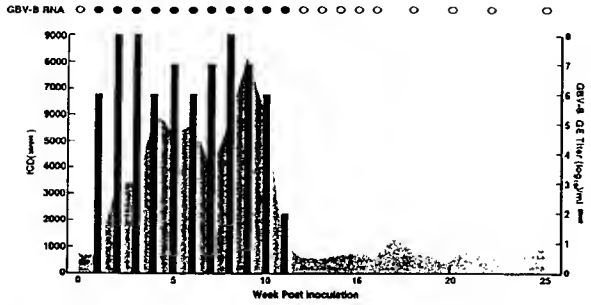
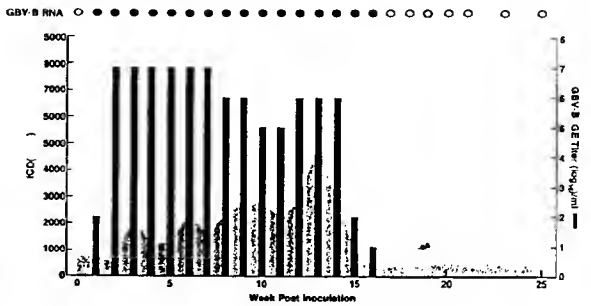

ATCC VR-806
10⁻² dilution
SM 661
GB 8/93
10⁻⁴ dilution
SM 749
10⁻⁵ dilution
SM 720
10⁻⁶ dilution
SM 737
GB 2/94
10⁻⁵ dilution
SM 760
10⁻⁶ dilution
SM 750
10⁻⁷ dilution
SM 769
10⁻⁶ dilution
SM 748
10⁻⁷ dilution
SM 799
10⁻⁷ dilution
SM 795
10⁻⁶ dilution
SM 782
10⁻⁷ dilution
SM 777
10⁻⁸dilution
SM 768
10⁻⁹ dilution
SM 787
10⁻⁹ dilution
SM 788
H205
2 x 10⁻¹ dilution
SM 42
SO 100
CT 11/91
5 x 10⁻¹ dilution
SM 670

FIG. 2

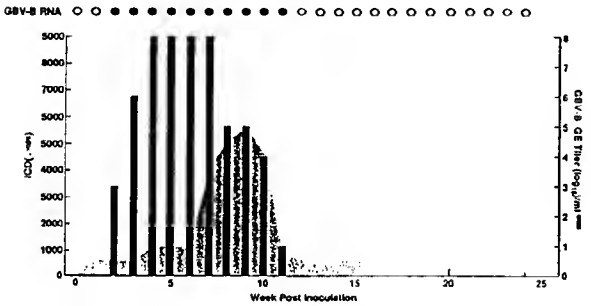
S. mystax 760: 10^{-5} Dilution



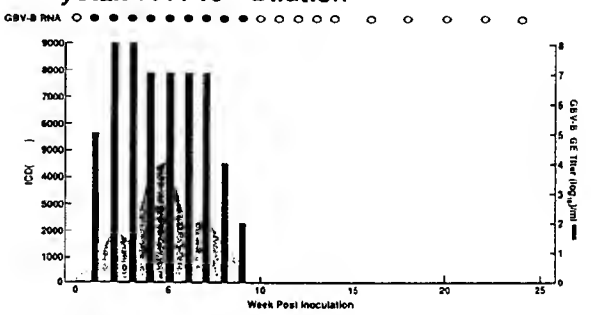
S. mystax 750: 10^{-6} Dilution



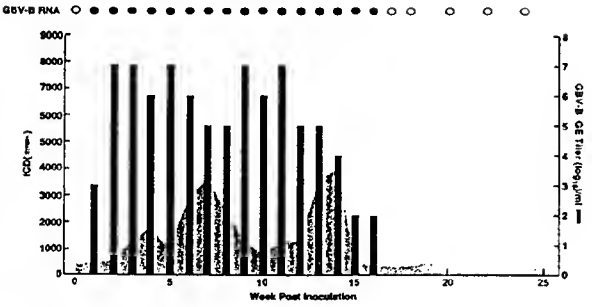
S. mystax 769: 10^{-7} Dilution



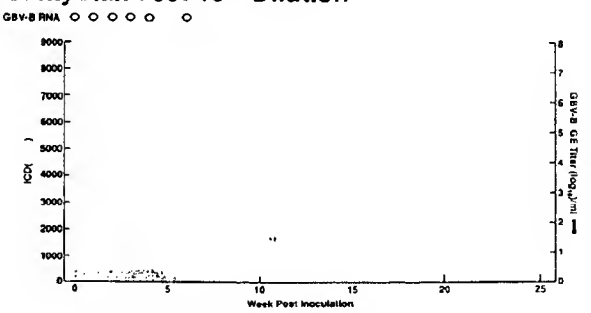
S. mystax 777: 10^{-7} Dilution



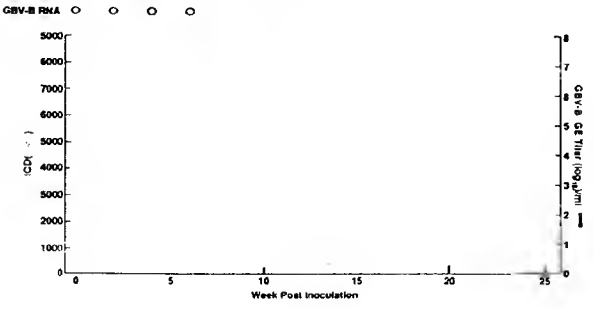
S. mystax 782: 10^{-8} Dilution



S. mystax 768: 10^{-8} Dilution



S. mystax 787: 10^{-9} Dilution



S. mystax 788: 10^{-9} Dilution

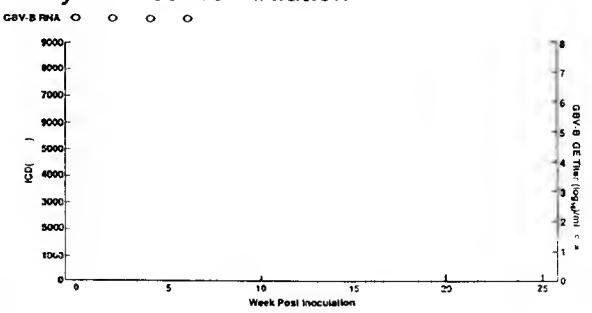


FIG. 3

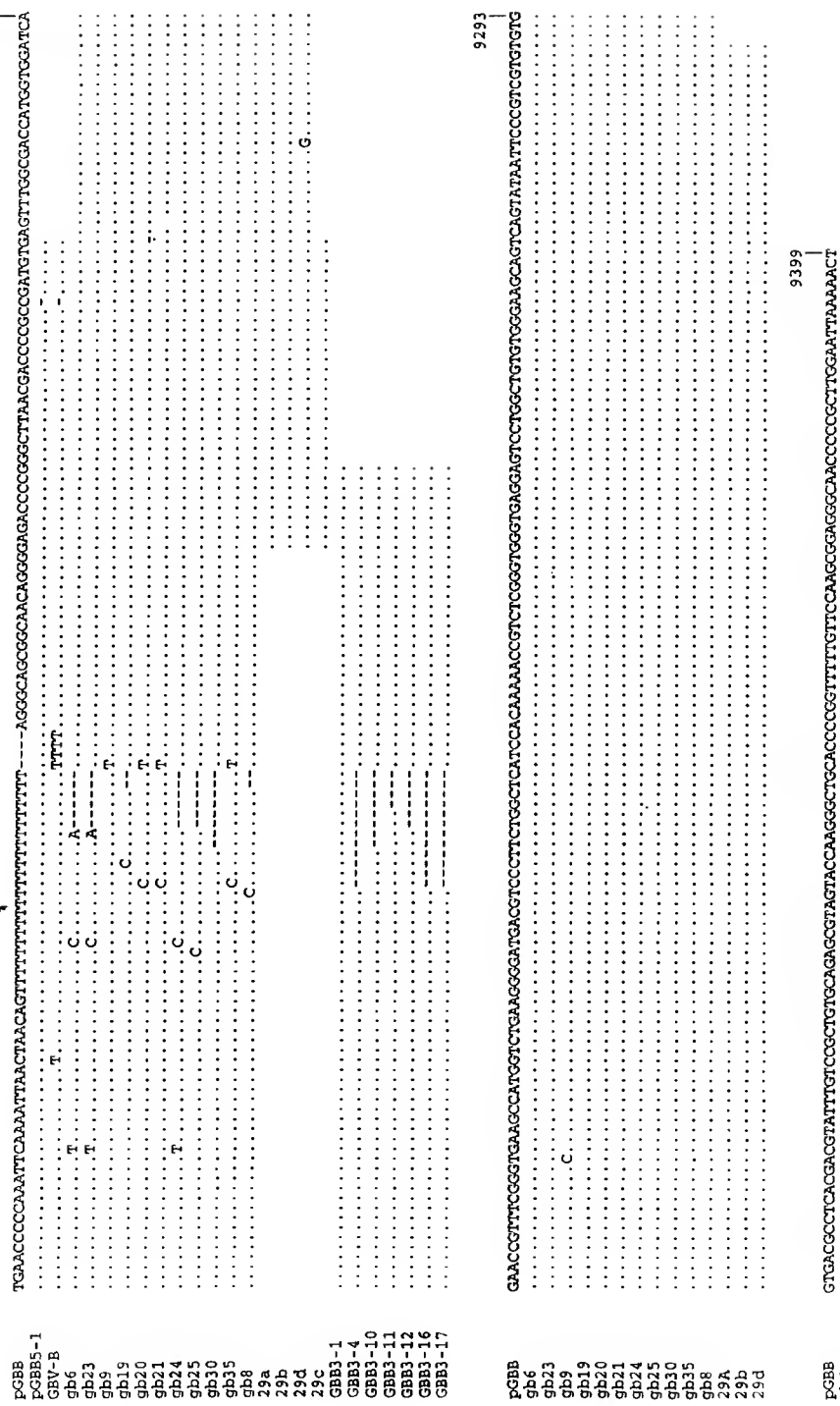

1
9163
pGBB
pGBB5-1
GBV-B
gb6
gb23
gb9
gb19
gb20
gb21
gb24
gb25
gb30
gb35
gb8
29a
29b
29d
29c
GBB3-1
GBB3-4
GBB3-10
GBB3-11
GBB3-12
GBB3-16
GBB3-17
9293
9399

FIG. 4

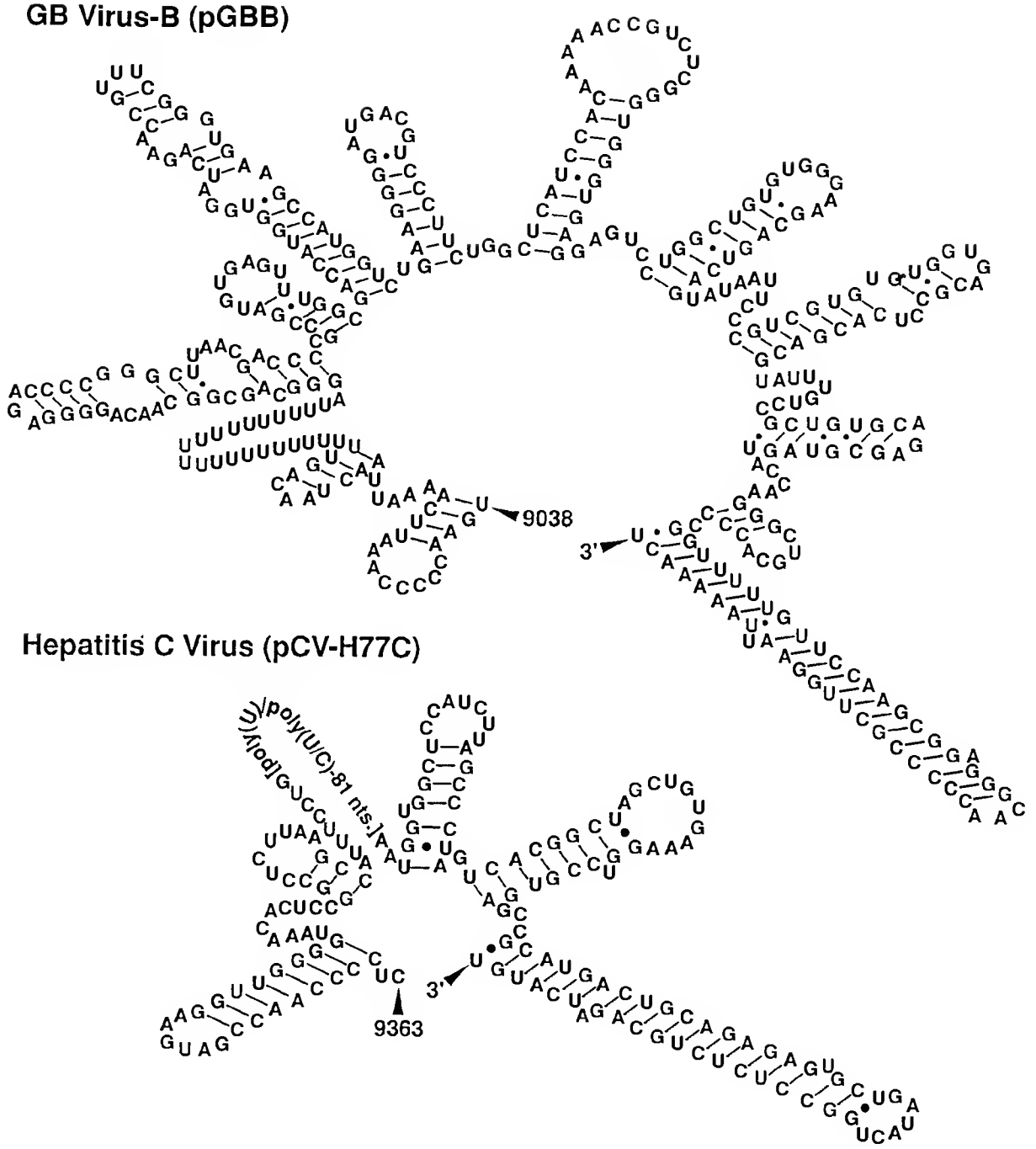
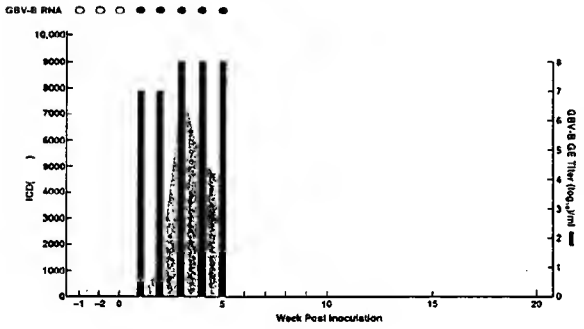
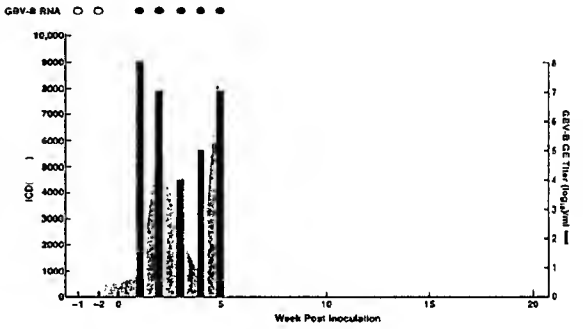

GB Virus-B (pGBB)
9038
3'
Hepatitis C Virus (pCV-H77C)
poly(U/C)-81 nts-IA
9363
3'

FIG. 5

S. mystax 816: RNA Transcripts of pGBB



S. mystax 817: RNA Transcripts of pGBB



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCCAGCCCCC	TGATGGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCCTCCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTTCTTG	200
GATAAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCCC	GCAAGACTGC	250
TAGCCGAGTA	GTGTTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GTCGCCCACA	400
GGACGTCAAG	TTCCCGGGTG	GCGGTCAGAT	CGTTGGTGGA	GTTTACTTGT	450
TGCCGCGCAG	GGGCCCTAGA	TTGGGTGTGC	GCGCGACGAG	GAAGACTTCC	500
GAGCGGTCGC	AACCTCGAGG	TAGACGTCAG	CCTATCCCCA	AGGCACGTCG	550
GCCCGAGGGC	AGGACCTGGG	CTCAGCCCGG	GTACCCTTGG	CCCCTCTATG	600
GCAATGAGGG	TTGCGGGTGG	GCGGGATGGC	TCCTGTCTCC	CCGTGGCTCT	650
CGGCCTAGCT	GGGGCCCCAC	AGACCCCCGG	CGTAGGTCGC	GCAATTTGGG	700
TAAGGTCATC	GATACCCTTA	CGTGCGGCTT	CGCCGACCTC	ATGGGGTACA	750
TACCGCTCGT	CGGCGCCCCT	CTTGGAGGCG	CTGCCAGGGC	CCTGGCGCAT	800
GGCGTCCGGG	TTCTGGAAGA	CGGCGTGAAC	TATGCAACAG	GGAACCTTCC	850
TGGTTGCTCT	TTCTCTATCT	TCCTTCTGGC	CCTGCTCTCT	TGCCTGACTG	900
TGCCCGCTTC	AGCCTACCAA	GTGCGCAATT	CCTCGGGGCT	TTACCATGTC	950
ACCAATGATT	GCCCTAACTC	GAGTATTGTG	TACGAGGCGG	CCGATGCCAT	1000
CCTGCACACT	CCGGGGTGTG	TCCCTTGCGT	TCGCGAGGGT	AACGCCTCGA	1050
GGTGTTGGGT	GGCGGTGACC	CCCACGGTGG	CCACCAGGGA	CGGCAAACTC	1100
CCCACAACGC	AGCTTCGACG	TCATATCGAT	CTGCTTGTCG	GGAGCGCCAC	1150
CCTCTGCTCG	GCCCTCTACG	TGGGGGACCT	GTGCGGGTCT	GTCTTTCTTG	1200
TTGGTCAACT	GTTTACCTTC	TCTCCCAGGC	GCCACTGGAC	GACGCAAGAC	1250
TGCAATTGTT	CTATCTATCC	CGGCCATATA	ACGGGTCATC	GCATGGCATG	1300
GGATATGATG	ATGAACTGGT	CCCCTACGGC	AGCGTTGGTG	GTAGCTCAGC	1350
TGCTCCGGAT	CCCACAAGCC	ATCATGGACA	TGATCGCTGG	TGCTCACTGG	1400
GGAGTCCTGG	CGGGCATAGC	GTATTTCTCC	ATGGTGGGGA	ACTGGGCGAA	1450
GGTCCTGGTA	GTGCTGCTGC	TATTTGCCGG	CGTCGACGCG	GAAACCCACG	1500
TCACCGGGGG	AAATGCCGGC	CGCACCACGG	CTGGGCTTGT	TGGTCTCCTT	1550
ACACCAGGCG	CCAAGCAGAA	CATCCAACTG	ATCAACACCA	ACGGCAGTTG	1600
GCACATCAAT	AGCACGGCCT	TGAATTGCAA	TGAAAGCCTT	AACACCGGCT	1650
GGTTAGCAGG	GCTCTTCTAT	CAACACAAAT	TCAACTCTTC	AGGCTGTCCT	1700
GAGAGGTTGG	CCAGCTGCCG	ACGCCTTACC	GATTTTGCCC	AGGGCTGGGG	1750
TCCTATCAGT	TATGCCAACG	GAAGCGGCCT	CGACGAACGC	CCCTACTGCT	1800
GGCACTACCC	TCCAAGACCT	TGTGGCATTG	TGCCCGCAAA	GAGCGTGTGT	1850
GGCCCGGTAT	ATTGCTTCAC	TCCCAGCCCC	GTGGTGGTGG	GAACGACCGA	1900

FIG. 6A

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CAGGTCGGGC	GCGCCTACCT	ACAGCTGGGG	TGCAAATGAT	ACGGATGTCT	1950
TCGTCCTTAA	CAACACCAGG	CCACCGCTGG	GCAATTGGTT	CGGTTGTACC	2000
TGGATGAACT	CAACTGGATT	CACCAAAGTG	TGCGGAGCGC	CCCCTTGTGT	2050
CATCGGAGGG	GTGGGCAACA	ACACCTTGCT	CTGCCCCACT	GATTGCTTCC	2100
GCAAACATCC	GGAAGCCACA	TACTCTCGGT	GCGGCTCCGG	TCCCTGGATT	2150
ACACCCAGGT	GCATGGTCGA	CTACCCGTAT	AGGCTTTGGC	ACTATCCTTG	2200
TACCATCAAT	TACACCATAT	TCAAAGTCAG	GATGTACGTG	GGAGGGGTCG	2250
AGCACAGGCT	GGAAGCGGCC	TGCAACTGGA	CGCGGGGCGA	ACGCTGTGAT	2300
CTGGAAGACA	GGGACAGGTC	CGAGCTCAGC	CCGTTGCTGC	TGTCCACCAC	2350
ACAGTGGCAG	GTCCTTCCGT	GTTCTTTCAC	GACCCTGCCA	GCCTTGTCCA	2400
CCGGCCTCAT	CCACCTCCAC	CAGAACATTG	TGGACGTGCA	GTACTTGTAC	2450
GGGGTAGGGT	CAAGCATCGC	GTCCTGGGCC	ATTAAGTGGG	AGTACGTCGT	2500
TCTCCTGTTC	CTTCTGCTTG	CAGACGCGCG	CGTCTGCTCC	TGCTTGTGGA	2550
TGATGTTACT	CATATCCCAA	GCGGAGGCGG	CTTTGGAGAA	CCTCGTAATA	2600
CTCAATGCAG	CATCCCTGGC	CGGGACGCAC	GGTCTTGTGT	CCTTCCTCGT	2650
GTTCTTCTGC	TTTGCGTGGT	ATCTGAAGGG	TAGGTGGGTG	CCCGGAGCGG	2700
TCTACGCCCT	CTACGGGATG	TGGCCTCTCC	TCCTGCTCCT	GCTGGCGTTG	2750
CCTCAGCGGG	CATACGCACT	GGACACGGAG	GTGGCCGCGT	CGTGTGGCGG	2800
CGTTGTTCTT	GTCGGGTTAA	TGGCGCTGAC	TCTGTCGCCA	TATTACAAGC	2850
GCTATATCAG	CTGGTGCATG	TGGTGGCTTC	AGTATTTTCT	GACCAGAGTA	2900
GAAGCGCAAC	TGCACGTGTG	GGTTCCCCCC	CTCAACGTCC	GGGGGGGGCG	2950
CGATGCCGTC	ATCTTACTCA	TGTGTGTAGT	ACACCCGACC	CTGGTATTTG	3000
ACATCACCAA	ACTACTCCTG	GCCATCTTCG	GACCCCTTTG	GATTCTTCAA	3050
GCCAGTTTGC	TTAAAGTCCC	CTACTTCGTG	CGCGTTCAAG	GCCTTCTCCG	3100
GATCTGCGCG	CTAGCGCGGA	AGATAGCCGG	AGGTCATTAC	GTGCAAATGG	3150
CCATCATCAA	GTTAGGGGCG	CTTACTGGCA	CCTATGTGTA	TAACCATCTC	3200
ACCCCTCTTC	GAGACTGGGC	GCACAACGGC	CTGCGAGATC	TGGCCGTGGC	3250
TGTGGAACCA	GTCGTCTTCT	CCCGAATGGA	GACCAAGCTC	ATCACGTGGG	3300
GGGCAGATAC	CGCCGCGTGC	GGTGACATCA	TCAACGGCTT	GCCCGTCTCT	3350
GCCCGTAGGG	GCCAGGAGAT	ACTGCTTGGG	CCAGCCGACG	GAATGGTCTC	3400
CAAGGGGTGG	AGGTTGCTGG	CGCCCATCAC	GGCGTACGCC	CAGCAGACGA	3450
GAGGCCTCCT	AGGGTGTATA	ATCACCAGCC	TGACTGGCCG	GGACAAAAAC	3500
CAAGTGGAGG	GTGAGGTCCA	GATCGTGTCA	ACTGCTACCC	AAACCTTCCT	3550
GGCAACGTGC	ATCAATGGGG	TATGCTGGAC	TCTGTACCAC	GGGGCCGGAA	3600
CGAGGACCAT	CGCATCACCC	AAGGGTCCTG	TCATCCAGAT	GTATACCAAT	3650
GTGGACCAAG	ACCTTGTGGG	CTGGCCCGCT	CCTCAAGGTT	CCCGCTCATT	3700
GACACCCTGT	ACCTGCGGCT	CCTCGGACCT	TTACCTGGTC	ACGAGGCACG	3750
CCGATGTCAT	TCCCGTGCGC	CGGCGAGGTG	ATAGCAGGGG	TAGCCTGCTT	3800

FIG. 6B

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCGCCCCGGC	CCATTTCCTA	CTTGAAAGGC	TCCTCGGGGG	GTCCGCTGTT	3850
GTGCCCCGCG	GGACACGCCG	TGGGCCTATT	CAGGGCCGCG	GTGTGCACCC	3900
GTGGAGTGGC	TAAAGCGGTG	GACTTTATCC	CTGTGGAGAA	CCTAGGGACA	3950
ACCATGAGAT	CCCCGGTGTT	CACGGACAAC	TCCTCTCCAC	CAGCAGTGCC	4000
CCAGAGCTTC	CAGGTGGCCC	ACCTGCATGC	TCCCACCGGC	AGCGGTAAGA	4050
GCACCAAGGT	CCCGGCTGCG	TACGCAGCCC	AGGGCTACAA	GGTGTTGGTG	4100
CTCAACCCCT	CTGTTGCTGC	AACGCTGGGC	TTTGGTGCTT	ACATGTCCAA	4150
GGCCCATGGG	GTTGATCCTA	ATATCAGGAC	CGGGGTGAGA	ACAATTACCA	4200
CTGGCAGCCC	CATCACGTAC	TCCACCTACG	GCAAGTTCCT	TGCCGACGGC	4250
GGGTGCTCAG	GAGGTGCTTA	TGACATAATA	ATTTGTGACG	AGTGCCACTC	4300
CACGGATGCC	ACATCCATCT	TGGGCATCGG	CACTGTCCTT	GACCAAGCAG	4350
AGACTGCGGG	GGCGAGACTG	GTTGTGCTCG	CCACTGCTAC	CCCTCCGGGC	4400
TCCGTCACTG	TGTCCCATCC	TAACATCGAG	GAGGTTGCTC	TGTCCACCAC	4450
CGGAGAGATC	CCCTTTTACG	GCAAGGCTAT	CCCCCTCGAG	GTGATCAAGG	4500
GGGGAAGACA	TCTCATCTTC	TGCCACTCAA	AGAAGAAGTG	CGACGAGCTC	4550
GCCGCGAAGC	TGGTCGCATT	GGGCATCAAT	GCCGTGGCCT	ACTACCGCGG	4600
TCTTGACGTG	TCTGTCATCC	CGACCAGCGG	CGATGTTGTC	GTCGTGTCGA	4650
CCGATGCTCT	CATGACTGGC	TTTACCGGCG	ACTTCGACTC	TGTGATAGAC	4700
TGCAACACGT	GTGTCACTCA	GACAGTCGAT	TTCAGCCTTG	ACCCTACCTT	4750
TACCATTGAG	ACAACCACGC	TCCCCCAGGA	TGCTGTCTCC	AGGACTCAAC	4800
GCCGGGGCAG	GACTGGCAGG	GGGAAGCCAG	GCATCTATAG	ATTTGTGGCA	4850
CCGGGGGAGC	GCCCCTCCGG	CATGTTCGAC	TCGTCCGTCC	TCTGTGAGTG	4900
CTATGACGCG	GGCTGTGCTT	GGTATGAGCT	CACGCCCGCC	GAGACTACAG	4950
TTAGGCTACG	AGCGTACATG	AACACCCCGG	GGCTTCCCGT	GTGCCAGGAC	5000
CATCTTGAAT	TTTGGGAGGG	CGTCTTTACG	GGCCTCACTC	ATATAGATGC	5050
CCACTTTTTA	TCCCAGACAA	AGCAGAGTGG	GGAGAACTTT	CCTTACCTGG	5100
TAGCGTACCA	AGCCACCGTG	TGCGCTAGGG	CTCAAGCCCC	TCCCCCATCG	5150
TGGGACCAGA	TGTGGAAGTG	TTTGATCCGC	CTTAAACCCA	CCCTCCATGG	5200
GCCAACACCC	CTGCTATACA	GACTGGGCGC	TGTTCAGAAT	GAAGTCACCC	5250
TGACGCACCC	AATCACCAAA	TACATCATGA	CATGCATGTC	GGCCGACCTG	5300
GAGGTCGTCA	CGAGCACCTG	GGTGCTCGTT	GGCGGCGTCC	TGGCTGCTCT	5350
GGCCGCGTAT	TGCCTGTCAA	CAGGCTGCGT	GGTCATAGTG	GGCAGGATCG	5400
TCTTGTCCGG	GAAGCCGGCA	ATTATACCTG	ACAGGGAGGT	TCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTGCTCTCAG	CACTTACCGT	ACATCGAGCA	5500
AGGGATGATG	CTCGCTGAGC	AGTTCAAGCA	GAAGGCCCTC	GGCCTCCTGC	5550
AGACCGCGTC	CCGCCATGCA	GAGGTTATCA	CCCCTGCTGT	CCAGACCAAC	5600
TGGCAGAAAC	TCGAGGTCTT	TTGGGCGAAG	CACATGTGGA	ATTTCATCAG	5650
TGGGATACAA	TACTTGGCGG	GCCTGTCAAC	GCTGCCTGGT	AACCCCGCCA	5700

FIG. 6C

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTGCTTCATT	GATGGCTTTT	ACAGCTGCCG	TCACCAGCCC	ACTAACCACT	5750
GGCCAAACCC	TCCTCTTCAA	CATATTGGGG	GGGTGGGTGG	CTGCCCAGCT	5800
CGCCGCCCCC	GGTGCCGCTA	CTGCCTTTGT	GGGTGCTGGC	CTAGCTGGCG	5850
CCGCCATCGG	CAGCGTTGGA	CTGGGGAAGG	TCCTCGTGGA	CATTCTTGCA	5900
GGGTATGGCG	CGGGCGTGGC	GGGAGCTCTT	GTAGCATTCA	AGATCATGAG	5950
CGGTGAGGTC	CCCTCCACGG	AGGACCTGGT	CAATCTGCTG	CCCGCCATCC	6000
TCTCGCCTGG	AGCCCTTGTA	GTCGGTGTGG	TCTGCGCAGC	AATACTGCGC	6050
CGGCACGTTG	GCCCGGGCGA	GGGGGCAGTG	CAATGGATGA	ACCGGCTAAT	6100
AGCCTTCGCC	TCCCGGGGGA	ACCATGTTTC	CCCCACGCAC	TACGTGCCGG	6150
AGAGCGATGC	AGCCGCCCGC	GTCACTGCCA	TACTCAGCAG	CCTCACTGTA	6200
ACCCAGCTCC	TGAGGCGACT	GCATCAGTGG	ATAAGCTCGG	AGTGTACCAC	6250
TCCATGCTCC	GGTTCCTGGC	TAAGGGACAT	CTGGGACTGG	ATATGCGAGG	6300
TGCTGAGCGA	CTTTAAGACC	TGGCTGAAAG	CCAAGCTCAT	GCCACAACTG	6350
CCTGGGATTC	CCTTTGTGTC	CTGCCAGCGC	GGGTATAGGG	GGGTCTGGCG	6400
AGGAGACGGC	ATTATGCACA	CTCGCTGCCA	CTGTGGAGCT	GAGATCACTG	6900
GACATGTCAA	AAACGGGACG	ATGAGGATCG	TCGGTCCTAG	GACCTGCAGG	6950
AACATGTGGA	GTGGGACGTT	CCCCATTAAC	GCCTACACCA	CGGGCCCCTG	6550
TACTCCCCTT	CCTGCGCCGA	ACTATAAGTT	CGCGCTGTGG	AGGGTGTCTG	6600
CAGAGGAATA	CGTGGAGATA	AGGCGGGTGG	GGGACTTCCA	CTACGTATCG	6650
GGTATGACTA	CTGACAATCT	TAAATGCCCG	TGCCAGATCC	CATCGCCCGA	6700
ATTTTTCACA	GAATTGGACG	GGGTGCGCCT	ACACAGGTTT	GCGCCCCCTT	6750
GCAAGCCCTT	GCTGCGGGAG	GAGGTATCAT	TCAGAGTAGG	ACTCCACGAG	6800
TACCCCGTGG	GGTCGCAATT	ACCTTGCGAG	CCCGAACCGG	ACGTAGCCGT	6850
GTTGACGTCC	ATGCTCACTG	ATCCCTCCCA	TATAACAGCA	GAGGCGGCCG	6900
GGAGAAGGTT	GGCGAGAGGG	TCACCCCCTT	CTATGGCCAG	CTCCTCGGCT	6950
AGCCAGCTGT	CCGCTCCATC	TCTCAAGGCA	ACTTGCACCG	CCAACCATGA	7000
CTCCCCTGAC	GCCGAGCTCA	TAGAGGCTAA	CCTCCTGTGG	AGGCAGGAGA	7050
TGGGCGGCAA	CATCACCAGG	GTTGAGTCAG	AGAACAAAGT	GGTGATTCTG	7100
GACTCCTTCG	ATCCGCTTGT	GGCAGAGGAG	GATGAGCGGG	AGGTCTCCGT	7150
ACCTGCAGAA	ATTCTGCGGA	AGTCTCGGAG	ATTCGCCCGG	GCCCTGCCCG	7200
TCTGGGCGCG	GCCGGACTAC	AACCCCCCGC	TAGTAGAGAC	GTGGAAAAAG	7250
CCTGACTACG	AACCACCTGT	GGTCCATGGC	TGCCCGCTAC	CACCTCCACG	7300
GTCCCCTCCT	GTGCCTCCGC	CTCGGAAAAA	GCGTACGGTG	GTCCTCACCG	7350
AATCAACCCT	ATCTACTGCC	TTGGCCGAGC	TTCCCACCAA	AAGTTTTGGC	7400
AGCTCCTCAA	CTTCCGGCAT	TACGGGCGAC	AATACGACAA	CATCCTCTGA	7450
GCCCGCCCCT	TCTGGCTGCC	CCCCCGACTC	CGACGTTGAG	TCCTATTCTT	7500
CCATGCCCCC	CCTGGAGGGG	GAGCCTGGGG	ATCCGGATCT	CAGCGACGGG	7550
TCATGGTCGA	CGGTCAGTAG	TGGGGCCGAC	ACGGAAGATG	TCGTGTGCTG	7600

FIG. 6D

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CTCAATGTCT	TATTCCTGGA	CAGGCGCACT	CGTCACCCCG	TGCGCTGCGG	7650
AAGAACAAAA	ACTGCCCATC	AACGCACTGA	GCAACTCGTT	GCTACGCCAT	7700
CACAATCTGG	TGTATTCCAC	CACTTCACGC	AGTGCTTGCC	AAAGGCAGAA	7750
GAAAGTCACA	TTTGACAGAC	TGCAAGTTCT	GGACAGCCAT	TACCAGGACG	7800
TGCTCAAGGA	GGTCAAAGCA	GCGGCGTCAA	AAGTGAAGGC	TAACTTGCTA	7850
TCCGTAGAGG	AAGCTTGCAG	CCTGACGCCC	CCACATTCAG	CCAAATCCAA	7900
GTTTGGCTAT	GGGGCAAAAG	ACGTCCGTTG	CCATCCCAGA	AAGGCCGTAG	7950
CCCACATCAA	CTCCGTGTGG	AAAGACCTTC	TGGAAGACAG	TGTAACACCA	8000
ATAGACACTA	CCATCATGGC	CAAGAACGAG	GTTTTCTGCG	TTCAGCCTGA	8050
GAAGGGGGGT	CGTAAGCCAG	CTCGTCTCAT	CGTGTTCCCC	GACCTGGGCG	8100
TGCGCGTGTG	CGAGAAGATG	GCCCTGTACG	ACGTGGTTAG	CAAGCTCCCC	8150
CTGGCCGTCA	TGGGAAGCTC	CTACGGATTC	CAATACTCAC	CAGGACAGCG	8200
GGTTGAATTC	CTCGTGCAAG	CGTGGAAGTC	CAAGAAGACC	CCGATGGGGT	8250
TCTCGTATGA	TACCCGCTGT	TTTGACTCCA	CAGTCACTGA	GAGCGACATC	8300
CGTACGGAGG	AGGCAATTTA	CCAATGTTGT	GACCTGGACC	CCCAAGCCCG	8350
CGTGGCCATC	AAGTCCCTCA	CTGAGAGGCT	TTATGTTGGG	GGCCCTCTTA	8400
CCAATTCAAG	GGGGGAAAAC	TGCGGCTACC	GCAGGTGCCG	CGCGAGCGGC	8450
GTACTGACAA	CTAGCTGTGG	TAACACCCTC	ACTTGCTACA	TCAAGGCCCG	8500
GGCAGCCTGT	CGAGCCGCAG	GGCTCCAGGA	CTGCACCATG	CTCGTGTGTG	8550
GCGACGACTT	AGTCGTTATC	TGTGAAAGTG	CGGGGGTCCA	GGAGGACGCG	8600
GCGAGCCTGA	GAGCCTTCAC	GGAGGCTATG	ACCAGGTACT	CCGCCCCCCC	8650
CGGGGACCCC	CCACAACCAG	AATACGACTT	GGAGCTTATA	ACATCATGCT	8700
CCTCCAACGT	GTCAGTCGCC	CACGACGGCG	CTGGAAAGAG	GGTCTACTAC	8750
CTTACCCGTG	ACCCTACAAC	CCCCCTCGCG	AGAGCCGCGT	GGGAGACAGC	8800
AAGACACACT	CCAGTCAATT	CCTGGCTAGG	CAACATAATC	ATGTTTGCCC	8850
CCACACTGTG	GGCGAGGATG	ATACTGATGA	CCCATTTCTT	TAGCGTCCTC	8900
ATAGCCAGGG	ATCAGCTTGA	ACAGGCTCTT	AACTGTGAGA	TCTACGGAGC	8950
CTGCTACTCC	ATAGAACCAC	TGGATCTACC	TCCAATCATT	CAAAGACTCC	9000
ATGGCCTCAG	CGCATTTTCA	CTCCACAGTT	ACTCTCCAGG	TGAAATCAAT	9050
AGGGTGGCCG	CATGCCTCAG	AAAACTTGGG	GTCCCGCCCT	TGCGAGCTTG	9100
GAGACACCGG	GCCCCGAGCG	TCCGCGCTAG	GCTTCTGTCC	AGAGGAGGCA	9150
GGGCTGCCAT	ATGTGGCAAG	TACCTCTTCA	ACTGGGCAGT	AAGAACAAAG	9200
CTCAAACTCA	CTCCAATAGC	GGCCGCTGGC	CGGCTGGACT	TGTCCGGTTG	9250
GTTCACGGCT	GGCTACAGCG	GGGGAGACAT	TTATCACAGC	GTGTCTCATG	9300
CCCGGCCCCG	CTGGTTCTGG	TTTTGCCTAC	TCCTGCTCGC	TGCAGGGGTA	9350
GGCATCTACC	TCCTCCCCAA	CCGATGAAGG	TTGGGGTAAA	CACTCCGGCC	9400
TCTTAAGCCA	TTTCCTGTTT	TTTTTTTTTT	TTTTTTTTTT	TTTTTCTTTT	9450
TTTTTTTCTT	TCCTTTCCTT	CTTTTTTTCC	TTTCTTTTTC	CCTTCTTTAA	9500

FIG. 6E

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TGGTGGCTCC	ATCTTAGCCC	TAGTCACGGC	TAGCTGTGAA	AGGTCCGTGA	9550
GCCGCATGAC	TGCAGAGAGT	GCTGATACTG	GCCTCTCTGC	AGATCATGT	9599

FIG. 6F

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
MSTNPKPQRK	TKRNTNRRPQ	DVKFPGGGQI	VGGVYLLPRR	GPRLGVRATR	50
KTSERSQPRG	RRQPIPKARR	PEGRTWAQPG	YPWPLYGNEG	CGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDTLTCGF	ADLMGYIPLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTVPAS	AYQVRNSSGL	200
YHVTNDCPNS	SIVYEAADAI	LHTPGCVPCV	REGNASRCWV	AVTPTVATRD	250
GKLPTTQLRR	HIDLLVGSAT	LCSALYVGDL	CGSVFLVGQL	FTFSPRRHWT	300
TQDCNCSIYP	GHITGHRMAW	DMMMNWSPTA	ALVVAQLLRI	PQAIMDMIAG	350
AHWGVLAGIA	YFSMVGNWAK	VLVVLLLFAG	VDAETHVTGG	NAGRTTAGLV	400
GLLTPGAKQN	IQLINTNGSW	HINSTALNCN	ESLNTGWLAG	LFYQHKFNSS	450
GCPERLASCR	RLTDFAQGWG	PISYANGSGL	DERPYCWHYP	PRPCGIVPAK	500
SVCGPVYCFT	PSPVVVGTTD	RSGAPTYSWG	ANDTDVFVLN	NTRPPLGNWF	550
GCTWMNSTGF	TKVCGAPPCV	IGGVGNNTLL	CPTDCFRKHP	EATYSRCGSG	600
PWITPRCMVD	YPYRLWHYPC	TINYTIFKVR	MYVGGVEHRL	EAACNWTRGE	650
RCDLEDRDRS	ELSPLLLSTT	QWQVLPCSFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSSIA	SWAIKWEYVV	LLFLLLADAR	VCSCLWMMLL	ISQAEAALEN	750
LVILNAASLA	GTHGLVSFLV	FFCFAWYLKG	RWVPGAVYAL	YGMWPLLLLL	800
LALPQRAYAL	DTEVAASCGG	VVLVGLMALT	LSPYYKRYIS	WCMWWLQYFL	850
TRVEAQLHVW	VPPLNVRGGR	DAVILLMCVV	HPTLVFDITK	LLLAIFGPLW	900
ILQASLLKVP	YFVRVQGLLR	ICALARKIAG	GHYVQMAIIK	LGALTGTYVY	950
NHLTPLRDWA	HNGLRDLAVA	VEPVVFSRME	TKLITWGADT	AACGDIINGL	1000
PVSARRGQEI	LLGPADGMVS	KGWRLLAPIT	AYAQQTRGLL	GCIITSLTGR	1050
DKNQVEGEVQ	IVSTATQTFL	ATCINGVCWT	VYHGAGTRTI	ASPKGPVIQM	1100
YTNVDQDLVG	WPAPQGSRSL	TPCTCGSSDL	YLVTRHADVI	PVRRRGDSRG	1150
SLLSPRPISY	LKGSSGGPLL	CPAGHAVGLF	RAAVCTRGVA	KAVDFIPVEN	1200
LETTMRSPVF	TDNSSPPAVP	QSFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGVDPNIRT	GVRTITTGSP	ITYSTYGKFL	1300
ADGGCSGGAY	DIIICDECHS	TDATSILGIG	TVLDQAETAG	ARLVVLATAT	1350
PPGSVTVSHP	NIEEVALSTT	GEIPFYGKAI	PLEVIKGGRH	LIFCHSKKKC	1400
DELAAKLVAL	GINAVAYYRG	LDVSVIPTSG	DVVVVSTDAL	MTGFTGDFDS	1450
VIDCNTCVTQ	TVDFSLDPTF	TIETTTLPQD	AVSRTQRRGR	TGRGKPGIYR	1500
FVAPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETTVRLR	AYMNTPGLPV	1550
CQDHLEFWEG	VFTGLTHIDA	HFLSQTKQSG	ENFPYLVAYQ	ATVCARAQAP	1600
PPSWDQMWKC	LIRLKPTLHG	PTPLLYRLGA	VQNEVTLTHP	ITKYIMTCMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLSTGCV	VTVGRIVLSG	KPAIIPDREV	1700
LYQEFDEMEE	CSQHLPYIEQ	GMMLAEQFKQ	KALGLLQTAS	RHAEVITPAV	1750
QTNWQKLEVF	WAKHMWNFIS	GIQYLAGLST	LPGNPAIASL	MAFTAAVTSP	1800
LTTGQTLLFN	ILGGWVAAQL	AAPGAATAFV	GAGLAGAAIG	SVGLGKVLVD	1850
ILAGYGAGVA	GALVAFKIMS	GEVPSTEDLV	NLLPAILSPG	ALVVGVVCAA	1900

FIG. 6G

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ILRRHVGPGE	GAVQWMNRLI	AFASRGNHVS	PTHYVPESDA	AARVTAILSS	1950
LTVTQLLRRL	HQWISSECTT	PCSGSWLRDI	WDWICEVLSD	FKTWLKAKLM	2000
PQLPGIPFVS	CQRGYRGVWR	GDGIMHTRCH	CGAEITGHVK	NGTMRIVGPR	2050
TCRNMWSGTF	PINAYTTGPC	TPLPAPNYKF	ALWRVSAEEY	VEIRRVGDFH	2100
YVSGMTTDNL	KCPCQIPSPE	FFTELDGVRL	HRFAPPCKPL	LREEVSFRVG	2150
LHEYPVGSQL	PCEPEPDVAV	LTSMLTDPSH	ITAEAAGRRL	ARGSPPSMAS	2200
SSASQLSAPS	LKATCTANHD	SPDAELIEAN	LLWRQEMGGN	ITRVESENKV	2250
VILDSFDPLV	AEEDEREVSV	PAEILRKSRR	FARALPVWAR	PDYNPPLVET	2300
WKKPDYEPPV	VHGCPLPPPR	SPPVPPPRKK	RTVVLTESTL	STALAELATK	2350
SFGSSSTSGI	TGDNTTTSSE	PAPSGCPPDS	DVESYSSMPP	LEGEPGDPDL	2400
SDGSWSTVSS	GADTEDVVCC	SMSYSWTGAL	VTPCAAEEQK	LPINALSNSL	2450
LRHHNLVYST	TSRSACQRQK	KVTFDRLQVL	DSHYQDVLKE	VKAAASKVKA	2500
NLLSVEEACS	LTPPHSAKSK	FGYGAKDVRC	HARKAVAHIN	SVWKDLLEDS	2550
VTPIDTTIMA	KNEVFCVQPE	KGGRKPARLI	VFPDLGVRVC	EKMALYDVVS	2600
KLPLAVMGSS	YGFQYSPGQR	VEFLVQAWKS	KKTPMGFSYD	TRCFDSTVTE	2650
SDIRTEEAIY	QCCDLDPQAR	VAIKSLTERL	YVGGPLTNSR	GENCGYRRCR	2700
ASGVLTTSCG	NTLTCYIKAR	AACRAAGLQD	CTMLVCGDDL	VVICESAGVQ	2750
EDAASLRAFT	EAMTRYSAPP	GDPPQPEYDL	ELITSCSSNV	SVAHDGAGKR	2800
VYYLTRDPTT	PLARAAWETA	RHTPVNSWLG	NIIMFAPTLW	ARMILMTHFF	2850
SVLIARDQLE	QALNCEIYGA	CYSIEPLDLP	PIIQRLHGLS	AFSLHSYSPG	2900
EINRVAACLR	KLGVPPLRAW	RHRARSVRAR	LLSRGGRAAI	CGKYLFNWAV	2950
RTKLKLTPIA	AAGRLDLSGW	FTAGYSGGDI	YHSVSHARPR	WFWFCLLLLA	3000
AGVGIYLLPN R					3011

FIG. 6H

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCCAGCCCCC	TGATGGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCCTCCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTTCTTG	200
GATCAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCCC	GCGAGACTGC	250
TAGCCGAGTA	GTGTTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GCCGCCCACA	400
GGACGTCAAG	TTCCCGGGCG	GTGGTCAGAT	CGTTGGTGGA	GTTTACCTGT	450
TGCCGCGCAG	GGGCCCCAGG	TTGGGTGTGC	GCGCGACTAG	GAAGGCTTCC	500
GAGCGGTCGC	AACCTCGTGG	AAGGCGACAA	CCTATCCCAA	AGGCTCGCCG	550
ACCCGAGGGC	AGGGCCTGGG	CTCAGCCCGG	GTACCCTTGG	CCCCTCTATG	600
GCAATGAGGG	CCTGGGGTGG	GCAGGATGGC	TCCTGTCACC	CCGCGGCTCC	650
CGGCCTAGTT	GGGGCCCCAC	GGACCCCCGG	CGTAGGTCGC	GTAACTTGGG	700
TAAGGTCATC	GATACCCTTA	CATGCGGCTT	CGCCGATCTC	ATGGGGTACA	750
TTCCGCTCGT	CGGCGCCCCC	CTAGGGGCGG	CTGCCAGGGC	CTTGGCACAC	800
GGTGTCCGGG	TTCTGGAGGA	CGGCGTGAAC	TATGCAACAG	GGAACTTGCC	850
CGGTTGCTCT	TTCTCTATCT	TCCTCTTGGC	TCTGCTGTCC	TGTTTGACCA	900
TCCCAGCTTC	CGCTTATGAA	GTGCGCAACG	TGTCCGGGAT	ATACCATGTC	950
ACGAACGACT	GCTCCAACTC	AAGCATTGTG	TATGAGGCAG	CGGACGTGAT	1000
CATGCATACT	CCCGGGTGCG	TGCCCTGTGT	TCAGGAGGGT	AACAGCTCCC	1050
GTTGCTGGGT	AGCGCTCACT	CCCACGCTCG	CGGCCAGGAA	TGCCAGCGTC	1100
CCCACTACGA	CAATACGACG	CCACGTCGAC	TTGCTCGTTG	GGACGGCTGC	1150
TTTCTGCTCC	GCTATGTACG	TGGGGGATCT	CTGCGGATCT	ATTTTCCTCG	1200
TCTCCCAGCT	GTTCACCTTC	TCGCCTCGCC	GGCATGAGAC	AGTGCAGGAC	1250
TGCAACTGCT	CAATCTATCC	CGGCCATGTA	TCAGGTCACC	GCATGGCTTG	1300
GGATATGATG	ATGAACTGGT	CACCTACAAC	AGCCCTAGTG	GTGTCGCAGT	1350
TGCTCCGGAT	CCCACAAGCT	GTCGTGGACA	TGGTGGCGGG	GGCCCACTGG	1400
GGAGTCCTGG	CGGGCCTTGC	CTACTATTCC	ATGGTAGGGA	ACTGGGCTAA	1450
GGTTCTGATT	GTGGCGCTAC	TCTTTGCCGG	CGTTGACGGG	GAGACCCACA	1500
CGACGGGGAG	GGTGGCCGGC	CACACCACCT	CCGGGTTCAC	GTCCCTTTTC	1550
TCATCTGGGG	CGTCTCAGAA	AATCCAGCTT	GTGAATACCA	ACGGCAGCTG	1600
GCACATCAAC	AGGACTGCCC	TAAATTGCAA	TGACTCCCTC	CAAACTGGGT	1650
TCTTTGCCGC	GCTGTTTTAC	GCACACAAGT	TCAACTCGTC	CGGGTGCCCG	1700
GAGCGCATGG	CCAGCTGCCG	CCCCATTGAC	TGGTTCGCCC	AGGGGTGGGG	1750
CCCCATCACC	TATACTAAGC	CTAACAGCTC	GGATCAGAGG	CCTTATTGCT	1800
GGCATTACGC	GCCTCGACCG	TGTGGTGTCG	TACCCGCGTC	GCAGGTGTGT	1850
GGTCCAGTGT	ATTGTTTCAC	CCCAAGCCCT	GTTGTGGTGG	GGACCACCGA	1900

FIG. 7A

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCGTTCCGGT	GTCCCTACGT	ATAGCTGGGG	GGAGAATGAG	ACAGACGTGA	1950
TGCTCCTCAA	CAACACGCGT	CCGCCACAAG	GCAACTGGTT	CGGCTGTACA	2000
TGGATGAATA	GTACTGGGTT	CACTAAGACG	TGCGGAGGTC	CCCCGTGTAA	2050
CATCGGGGGG	GTCGGTAACC	GCACCTTGAT	CTGCCCCACG	GACTGCTTCC	2100
GGAAGCACCC	CGAGGCTACT	TACACAAAAT	GTGGCTCGGG	GCCCTGGTTG	2150
ACACCTAGGT	GCCTAGTAGA	CTACCCATAC	AGGCTTTGGC	ACTACCCCTG	2200
CACTCTCAAT	TTTTCCATCT	TTAAGGTTAG	GATGTATGTG	GGGGGCGTGG	2250
AGCACAGGCT	CAATGCCGCA	TGCAATTGGA	CTCGAGGAGA	GCGCTGTAAC	2300
TTGGAGGACA	GGGATAGGTC	AGAACTCAGC	CCGCTGCTGC	TGTCTACAAC	2350
AGAGTGGCAG	ATACTGCCCT	GTGCTTTCAC	CACCCTACCG	GCTTTATCCA	2400
CTGGTTTGAT	CCATCTCCAT	CAGAACATCG	TGGACGTGCA	ATACCTGTAC	2450
GGTGTAGGGT	CAGCGTTTGT	CTCCTTTGCA	ATCAAATGGG	AGTACATCCT	2500
GTTGCTTTTC	CTTCTCCTGG	CAGACGCGCG	CGTGTGTGCC	TGCTTGTGGA	2550
TGATGCTGCT	GATAGCCCAG	GCTGAGGCCG	CCTTAGAGAA	CTTGGTGGTC	2600
CTCAATGCGG	CGTCCGTGGC	CGGAGCGCAT	GGTATTCTCT	CCTTTCTTGT	2650
GTTCTTCTGC	GCCGCCTGGT	ACATTAAGGG	CAGGCTGGCT	CCTGGGGCGG	2700
CGTATGCTTT	TTATGGCGTA	TGGCCGCTGC	TCCTGCTCCT	ACTGGCGTTA	2750
CCACCACGAG	CTTACGCCTT	GGACCGGGAG	ATGGCTGCAT	CGTGCGGGGG	2800
TGCGGTTCTT	GTAGGTCTGG	TATTCTTGAC	CTTGTCACCA	TACTACAAAG	2850
TGTTTCTCAC	TAGGCTCATA	TGGTGGTTAC	AATACTTTAT	CACCAGAGCC	2900
GAGGCGCACA	TGCAAGTGTG	GGTCCCCCCC	CTCAACGTTC	GGGGAGGCCG	2950
CGATGCCATC	ATCCTCCTCA	CGTGTGCGGT	TCATCCAGAG	TTAATTTTTG	3000
ACATCACCAA	ACTCCTGCTC	GCCATACTCG	GCCCGCTCAT	GGTGCTCCAG	3050
GCTGGCATAA	CGAGAGTGCC	GTACTTCGTG	CGCGCTCAAG	GGCTCATTCG	3100
TGCATGCATG	TTAGTGCGAA	AAGTCGCCGG	GGGTCATTAT	GTCCAAATGG	3150
TCTTCATGAA	GCTGGGCGCG	CTGACAGGTA	CGTACGTTTA	TAACCATCTT	3200
ACCCCACTGC	GGGACTGGGC	CCACGCGGGC	CTACGAGACC	TTGCGGTGGC	3250
GGTAGAGCCC	GTCGTCTTCT	CCGCCATGGA	GACCAAGGTC	ATCACCTGGG	3300
GAGCAGACAC	CGCTGCGTGT	GGGGACATCA	TCTTGGGTCT	ACCCGTCTCC	3350
GCCCGAAGGG	GGAAGGAGAT	ATTTTTGGGA	CCGGCTGATA	GTCTCGAAGG	3400
GCAAGGGTGG	CGACTCCTTG	CGCCCATCAC	GGCCTACTCC	CAACAAACGC	3450
GGGGCGTACT	TGGTTGCATC	ATCACTAGCC	TCACAGGCCG	GGACAAGAAC	3500
CAGGTCGAAG	GGGAGGTTCA	AGTGGTTTCT	ACCGCAACAC	AATCTTTCCT	3550
GGCGACCTGC	ATCAACGGCG	TGTGCTGGAC	TCTCTACCAT	GGCGCTGGCT	3600
CGAAGACCCT	AGCCGGTCCA	AAAGGTCCAA	TCACCCAAAT	GTACACCAAT	3650
GTAGACCTGG	ACCTCGTCGG	CTGGCAGGCG	CCCCCCGGGG	CGCGCTCCAT	3700
GACACCATGC	AGCTGTGGCA	GCTCGGACCT	TTACTTGGTC	ACGAGACATG	3750
CTGATGTCAT	TCCGGTGCGC	CGGCGAGGCG	ACAGCAGGGG	AAGTCTACTC	3800

FIG. 7B

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCCCCCAGGC	CCGTCTCCTA	CCTGAAAGGC	TCCTCGGGTG	GTCCATTGCT	3850
TTGCCCTTCG	GGGCACGTCG	TGGGCGTCTT	CCGGGCTGCT	GTGTGCACCC	3900
GGGGGGTCGC	GAAGGCGGTG	GACTTCATAC	CCGTTGAGTC	TATGGAAACT	3950
ACCATGCGGT	CTCCGGTCTT	CACAGACAAC	TCAACCCCCC	CGGCTGTACC	4000
GCAGACATTC	CAAGTGGCAC	ATCTGCACGC	TCCTACTGGC	AGCGGCAAGA	4050
GCACCAAAGT	GCCGGCTGCG	TATGCAGCCC	AAGGGTACAA	GGTGCTCGTC	4100
CTGAACCCGT	CCGTTGCCGC	CACCTTAGGG	TTTGGGGCGT	ATATGTCCAA	4150
GGCACACGGT	ATCGACCCTA	ACATCAGAAC	TGGGGTAAGG	ACCATTACCA	4200
CGGGCGGCTC	CATTACGTAC	TCCACCTATG	GCAAGTTCCT	TGCCGACGGT	4250
GGCTGTTCTG	GGGGCGCCTA	TGACATCATA	ATATGTGATG	AGTGCCACTC	4300
AACTGACTCG	ACTACCATCT	TGGGCATCGG	CACAGTCCTG	GACCAAGCGG	4350
AGACGGCTGG	AGCGCGGCTC	GTCGTGCTCG	CCACCGCTAC	ACCTCCGGGA	4400
TCGGTTACCG	TGCCACACCC	CAATATCGAG	GAAATAGGCC	TGTCCAACAA	4450
TGGAGAGATC	CCCTTCTATG	GCAAAGCCAT	CCCCATTGAG	GCCATCAAGG	4500
GGGGGAGGCA	TCTCATTTTC	TGCCATTCCA	AGAAGAAATG	TGACGAGCTC	4550
GCCGCAAAGC	TGACAGGCCT	CGGACTGAAC	GCTGTAGCAT	ATTACCGGGG	4600
CCTTGATGTG	TCCGTCATAC	CGCCTATCGG	AGACGTCGTT	GTCGTGGCAA	4650
CAGACGCTCT	AATGACGGGT	TTCACCGGCG	ATTTTGACTC	AGTGATCGAC	4700
TGCAATACAT	GTGTCACCCA	GACAGTCGAC	TTCAGCTTGG	ATCCCACCTT	4750
CACCATTGAG	ACGACGACCG	TGCCCCAAGA	CGCGGTGTCG	CGCTCGCAAC	4800
GGCGAGGTAG	AACTGGCAGG	GGTAGGAGTG	GCATCTACAG	GTTTGTGACT	4850
CCAGGAGAAC	GGCCCTCGGG	CATGTTCGAT	TCTTCGGTCC	TGTGTGAGTG	4900
CTATGACGCG	GGCTGTGCTT	GGTATGAGCT	CACGCCCGCT	GAGACCTCGG	4950
TTAGGTTGCG	GGCTTACCTA	AATACACCAG	GGTTGCCCGT	CTGCCAGGAC	5000
CATCTGGAGT	TCTGGGAGAG	CGTCTTCACA	GGCCTCACCC	ACATAGATGC	5050
CCACTTCCTG	TCCCAGACTA	AACAGGCAGG	AGACAACTTT	CCTTACCTGG	5100
TGGCATATCA	AGCTACAGTG	TGCGCCAGGG	CTCAAGCTCC	ACCTCCATCG	5150
TGGGACCAAA	TGTGGAAGTG	TCTCATACGG	CTGAAACCTA	CACTGCACGG	5200
GCCAACACCC	CTGCTGTATA	GGCTAGGAGC	CGTCCAAAAT	GAGGTCATCC	5250
TCACACACCC	CATAACTAAA	TACATCATGG	CATGCATGTC	GGCTGACCTG	5300
GAGGTCGTCA	CTAGCACCTG	GGTGCTGGTA	GGCGGAGTCC	TTGCAGCTTT	5350
GGCCGCATAC	TGCCTGACGA	CAGGCAGTGT	GGTCATTGTG	GGCAGGATCA	5400
TCTTGTCCGG	GAAGCCAGCT	GTCGTTCCCG	ACAGGGAAGT	CCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTGTGCCTCA	CAACTTCGTT	ACATCGAGCA	5500
GGGAATGCAG	CTCGCCGAGC	AATTCAAGCA	AAAGGCGCTC	GGGTTGTTGC	5550
AAACGGCCAC	CAAGCAAGCG	GAGGCTGCTG	CTCCCGTGGT	GGAGTCCAAG	5600
TGGCGAGCCC	TTGAGACCTT	CTGGGCGAAG	CACATGTGGA	ATTTCATCAG	5650
CGGAATACAG	TACCTAGCAG	GCTTATCCAC	TCTGCCTGGA	AACCCCGCGA	5700

FIG. 7C

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TAGCATCATT	GATGGCATTT	ACAGCTTCTA	TCACTAGCCC	GCTCACCACC	5750
CAAAACACCC	TCCTGTTTAA	CATCTTGGGG	GGATGGGTGG	CTGCCCAACT	5800
CGCTCCTCCC	AGCGCTGCGT	CAGCTTTCGT	GGGCGCCGGC	ATCGCCGGAG	5850
CGGCTGTTGG	CAGCATAGGC	CTTGGGAAGG	TGCTCGTGGA	CATCTTGGCG	5900
GGCTATGGGG	CAGGGGTAGC	CGGCGCACTC	GTGGCCTTTA	AGGTCATGAG	5950
CGGCGAGGTG	CCCTCCACCG	AGGACCTGGT	CAACTTACTC	CCTGCCATCC	6000
TCTCTCCTGG	TGCCCTGGTC	GTCGGGGTCG	TGTGCGCAGC	AATACTGCGT	6050
CGGCACGTGG	GCCCGGGAGA	GGGGGCTGTG	CAGTGGATGA	ACCGGCTGAT	6100
AGCGTTCGCT	TCGCGGGGTA	ACCACGTCTC	CCCTACGCAC	TATGTGCCTG	6150
AGAGCGACGC	TGCAGCACGT	GTCACTCAGA	TCCTCTCTAG	CCTTACCATC	6200
ACTCAACTGC	TGAAGCGGCT	CCACCAGTGG	ATTAATGAGG	ACTGCTCTAC	6250
GCCATGCTCC	GGCTCGTGGC	TAAGGGATGT	TTGGGATTGG	ATATGCACGG	6300
TGTTGACTGA	CTTCAAGACC	TGGCTCCAGT	CCAAACTCCT	GCCGCGGTTA	6350
CCGGGAGTCC	CTTTCCTGTC	ATGCCAACGC	GGGTACAAGG	GAGTCTGGCG	6400
GGGGGACGGC	ATCATGCAAA	CCACCTGCCC	ATGCGGAGCA	CAGATCGCCG	6450
GACATGTCAA	AAACGGTTCC	ATGAGGATCG	TAGGGCCTAG	AACCTGCAGC	6500
AACACGTGGC	ACGGAACGTT	CCCCATCAAC	GCATACACCA	CGGGACCTTG	6550
CACACCCTCC	CCGGCGCCCA	ACTATTCCAG	GGCGCTATGG	CGGGTGGCTG	6600
CTGAGGAGTA	CGTGGAGGTT	ACGCGTGTGG	GGGATTTCCA	CTACGTGACG	6650
GGCATGACCA	CTGACAACGT	AAAGTGCCCA	TGCCAGGTTC	CGGCCCCCGA	6700
ATTCTTCACG	GAGGTGGATG	GAGTGCGGTT	GCACAGGTAC	GCTCCGGCGT	6750
GCAAACCTCT	TCTACGGGAG	GACGTCACGT	TCCAGGTCGG	GCTCAACCAA	6800
TACTTGGTCG	GGTCGCAGCT	CCCATGCGAG	CCCGAACCGG	ACGTAACAGT	6850
GCTTACTTCC	ATGCTCACCG	ATCCCTCCCA	CATTACAGCA	GAGACGGCTA	6900
AGCGTAGGCT	GGCTAGAGGG	TCTCCCCCCT	CTTTAGCCAG	CTCATCAGCT	6950
AGCCAGTTGT	CTGCGCCTTC	TTTGAAGGCG	ACATGCACTA	CCCACCATGA	7000
CTCCCCGGAC	GCTGACCTCA	TCGAGGCCAA	CCTCTTGTGG	CGGCAGGAGA	7050
TGGGCGGAAA	CATCACTCGC	GTGGAGTCAG	AGAATAAGGT	AGTAATTCTG	7100
GACTCTTTCG	AACCGCTTCA	CGCGGAGGGG	GATGAGAGGG	AGATATCCGT	7150
CGCGGCGGAG	ATCCTGCGAA	AATCCAGGAA	GTTCCCCTCA	GCGTTGCCCA	7200
TATGGGCACG	CCCGGACTAC	AATCCTCCAC	TGCTAGAGTC	CTGGAAGGAC	7250
CCGGACTACG	TCCCTCCGGT	GGTACACGGA	TGCCCATTGC	CACCTACCAA	7300
GGCTCCTCCA	ATACCACCTC	CACGGAGAAA	GAGGACGGTT	GTCCTGACAG	7350
AATCCAATGT	GTCTTCTGCC	TTGGCGGAGC	TCGCCACTAA	GACCTTCGGT	7400
AGCTCCGGAT	CGTCGGCCGT	TGATAGCGGC	ACGGCGACCG	CCCTTCCTGA	7450
CCTGGCCTCC	GACGACGGTG	ACAAAGGATC	CGACGTTGAG	TCGTACTCCT	7500
CCATGCCCCC	CCTTGAAGGG	GAGCCGGGGG	ACCCCGATCT	CAGCGACGGG	7550
TCTTGGTCTA	CCGTGAGTGA	GGAGGCTAGT	GAGGATGTCG	TCTGCTGCTC	7600

FIG. 7D

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AATGTCCTAT	ACGTGGACAG	GCGCCCTGAT	CACGCCATGC	GCTGCGGAGG	7650
AAAGTAAGCT	GCCCATCAAC	CCGTTGAGCA	ACTCTTTGCT	GCGTCACCAC	7700
AACATGGTCT	ACGCCACAAC	ATCCCCGCAGC	GCAAGCCTCC	GGCAGAAGAA	7750
GGTCACCTTT	GACAGATTGC	AAGTCCTGGA	TGATCATTAC	CGGGACGTAC	7800
TCAAGGAGAT	GAAGGCGAAG	GCGTCCACAG	TTAAGGCTAA	GCTTCTATCT	7850
ATAGAGGAGG	CCTGCAAGCT	GACGCCCCCA	CATTCGGCCA	AATCCAAATT	7900
TGGCTATGGG	GCAAAGGACG	TCCGGAACCT	ATCCAGCAGG	GCCGTTAACC	7950
ACATCCGCTC	CGTGTGGGAG	GACTTGCTGG	AAGACACTGA	AACACCAATT	8000
GACACCACCA	TCATGGCAAA	AAGTGAGGTT	TTCTGCGTCC	AACCAGAGAA	8050
GGGAGGCCGC	AAGCCAGCTC	GCCTTATCGT	ATTCCCAGAC	CTGGGAGTTC	8100
GTGTATGCGA	GAAGATGGCC	CTTTACGACG	TGGTCTCCAC	CCTTCCTCAG	8150
GCCGTGATGG	GCTCCTCATA	CGGATTTCAA	TACTCCCCCA	AGCAGCGGGT	8200
CGAGTTCCTG	GTGAATACCT	GGAAATCAAA	GAAATGCCCT	ATGGGCTTCT	8250
CATATGACAC	CCGCTGTTTT	GACTCAACGG	TCACTGAGAG	TGACATTCGT	8300
GTTGAGGAGT	CAATTTACCA	ATGTTGTGAC	TTGGCCCCCG	AGGCCAGACA	8350
GGCCATAAGG	TCGCTCACAG	AGCGGCTTTA	CATCGGGGGT	CCCCTGACTA	8400
ACTCAAAAGG	GCAGAACTGC	GGTTATCGCC	GGTGCCGCGC	AAGTGGCGTG	8450
CTGACGACTA	GCTGCGGTAA	TACCCTCACA	TGTTACTTGA	AGGCCACTGC	8500
AGCCTGTCGA	GCTGCAAAGC	TCCAGGACTG	CACGATGCTC	GTGAACGGAG	8550
ACGACCTTGT	CGTTATCTGT	GAAAGCGCGG	GAACCCAGGA	GGATGCGGCG	8600
GCCCTACGAG	CCTTCACGGA	GGCTATGACT	AGGTATTCCG	CCCCCCCCGG	8650
GGATCCGCCC	CAACCAGAAT	ACGACCTGGA	GCTGATAACA	TCATGTTCCT	8700
CCAATGTGTC	AGTCGCGCAC	GATGCATCTG	GCAAAAGGGT	ATACTACCTC	8750
ACCCGTGACC	CCACCACCCC	CCTTGCACGG	GCTGCGTGGG	AGACAGCTAG	8800
ACACACTCCA	ATCAACTCTT	GGCTAGGCAA	TATCATCATG	TATGCGCCCA	8850
CCCTATGGGC	AAGGATGATT	CTGATGACTC	ACTTTTTCTC	CATCCTTCTA	8900
GCTCAAGAGC	AACTTGAAAA	AGCCCTGGAT	TGTCAGATCT	ACGGGGCTTG	8950
CTACTCCATT	GAGCCACTTG	ACCTACCTCA	GATCATTGAA	CGACTCCATG	9000
GTCTTAGCGC	ATTTACACTC	CACAGTTACT	CTCCAGGTGA	GATCAATAGG	9050
GTGGCTTCAT	GCCTCAGGAA	ACTTGGGGTA	CCACCCTTGC	GAACCTGGAG	9100
ACATCGGGCC	AGAAGTGTCC	GCGCTAAGCT	ACTGTCCCAG	GGGGGGAGGG	9150
CCGCCACTTG	TGGCAGATAC	CTCTTTAACT	GGGCAGTAAG	GACCAAGCTT	9200
AAACTCACTC	CAATCCCGGC	CGCGTCCCAG	CTGGACTTGT	CTGGCTGGTT	9250
CGTCGCTGGT	TACAGCGGGG	GAGACATATA	TCACAGCCTG	TCTCGTGCCC	9300
GACCCCGCTG	GTTTCCGTTG	TGCCTACTCC	TACTTTCTGT	AGGGGTAGGC	9350
ATTTACCTGC	TCCCCAACCG	ATGAACGGGG	AGCTAACCAC	TCCAGGCCTT	9400
AAGCCATTTC	CTGTTTTTTT	TTTTTTTTTT	TTTTTTTTTT	TCTTTTTTTT	9450
TTTCTTTCCT	TTCCTTCTTT	TTTTCCTTTC	TTTTTCCCTT	CTTTAATGGT	9500

FIG. 7E

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GGCTCCATCT	TAGCCCTAGT	CACGGCTAGC	TGTGAAAGGT	CCGTGAGCCG	9550
CATGACTGCA	GAGAGTGCTG	ATACTGGCCT	CTCTGCAGAT	CATGT	9595

FIG. 7F

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
MSINPKPQRK	TKRNINRRPQ	DVKFPGGGQI	VGGVYLLPRR	GPRLGVRATR	50
KASERSQPRG	RRQPIPKARR	PEGRAWAQPG	YPWPLYGNEG	LGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDTLTCGF	ADLMGYIPLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTIPAS	AYEVRNVSGI	200
YHVINDCSNS	SIVYEAADVI	MHTPGCVPCV	QEGNSSRCWV	ALTPTLAARN	250
ASVPTTTTRR	HVDLLVGTAA	FCSAMYVGDL	CGSIFLVSQL	FTFSPRRHET	300
VQDCNCSIYP	GHVSGHRMAW	DMMMNWSPTT	ALVVSQLLRI	PQAVVDMVAG	350
AHWGVLAGLA	YYSMVGNWAK	VLIVALLFAG	VDGEIHTTGR	VAGHTTSGFT	400
SLFSSGASQK	IQLVNTNGSW	HINRTALNCN	DSLQTGFFAA	LFYAHKFNSS	450
GCPERMASCR	PIDWFAQGWG	PITYTKPNSS	DQRPYCWHYA	PRPCGVVPAS	500
QVCGPVYCFT	PSPVVVGTTD	RSGVPTYSWG	ENETDVMLLN	NTRPPQGNWF	550
GCTWMNSTGF	TKTCGGPPCN	IGGVGNRTLI	CPTDCFRKHP	EATYTKCGSG	600
PWLTPRCLVD	YPYRLWHYPC	TLNFSIFKVR	MYVGGVEHRL	NAACNWTRGE	650
RCNLEDRDRS	ELSPLLLSTT	EWQILPCAFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSAFV	SFAIKWEYIL	LLFLLLADAR	VCACLWMML	IAQAEAALEN	750
LVVLNAASVA	GAHGILSFLV	FFCAAWYIKG	RLAPGAAYAF	YGVWPLLLLL	800
LALPPRAYAL	DREMAASCGG	AVLVGLVFLT	LSPYYKVFLT	RLIWWLQYFI	850
TRAEAHMQVW	VPPLNVRGGR	DAIILLTCAV	HPELIFDITK	LLLAILGPLM	900
VLQAGITRVP	YFVRAQGLIR	ACMLVRKVAG	GHYVQMVFMK	LGALTGTYVY	950
NHLTPLRDWA	HAGLRDLAVA	VEPVVFSAME	TKVITWGADT	AACGDIILGL	1000
PVSARRGKEI	FLGPADSLEG	QGWRLLAPIT	AYSQQTRGVL	GCIITSLTGR	1050
DKNQVEGEVQ	VVSTATQSFL	ATCINGVCWT	VYHGAGSKTL	AGPKGPITQM	1100
YTNVDLDLVG	WQAPPGARSM	TPCSCGSSDL	YLVTRHADVI	PVRRRGDSRG	1150
SLLSPRPVSY	LKGSSGGPLL	CPSGHVVGVF	RAAVCTRGVA	KAVDFIPVES	1200
METTMRSPVF	TDNSTPPAVP	QTFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGIDPNIRT	GVRTITTGGS	ITYSTYGKFL	1300
ADGGCSGGAY	DIIICDECHS	TDSTTILGIG	TVLDQAETAG	ARLVVLATAT	1350
PPGSVTVPHP	NIEEIGLSNN	GEIPFYGKAI	PIEAIKGGRH	LIFCHSKKKC	1400
DELAAKLTGL	GLNAVAYYRG	LDVSVIPPIG	DVVVVATDAL	MTGFTGDFDS	1450
VIDCNTCVTQ	TVDFSLDPTF	TIETTTVPQD	AVSRSQRRGR	TGRGRSGIYR	1500
FVTPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETSVRLR	AYLNTPGLPV	1550
CQDHLEFWES	VFTGLTHIDA	HFLSQTKQAG	DNFPYLVAYQ	ATVCARAQAP	1600
PPSWDQMWKC	LIRLKPTLHG	PTPLLYRLGA	VQNEVILTHP	ITKYIMACMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLTTGSV	VIVGRIILSG	KPAVVPDREV	1700
LYQEFDEMEE	CASQLPYIEQ	GMQLAEQFKQ	KALGLLQTAT	KQAEAAAPVV	1750
ESKWRALETF	WAKHMWNFIS	GIQYLAGLST	LPGNPAIASL	MAFTASITSP	1800
LTTQNTLLFN	ILGGWVAAQL	APPSAASAFV	GAGIAGAAVG	SIGLGKVLVD	1850
ILAGYGAGVA	GALVAFKVMS	GEVPSTEDLV	NLLPAILSPG	ALVVGVVCAA	1900

FIG. 7G

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ILRRHVGPGE	GAVQWMNRLI	AFASRGNHVS	PIHYVPESDA	AARVIQILSS	1950
LTITQLLKRL	HQWINEDCST	PCSGSWLRDV	WDWICIVLID	FKIWLQSKLL	2000
PRLPGVPFLS	CQRGYKGVWR	GDGIMQTTCP	CGAQIAGHVK	NGSMRIVGPR	2050
TCSNIWHGTF	PINAYTIGPC	TPSPAPNYSR	ALWRVAAEEY	VEVIRVGDFH	2100
YVIGMITIDN	KCPCQVPAPE	FFTEVDGVRL	HRYAPACKPL	LREDVTFQVG	2150
LNQYLVGSQL	PCEPEPDVIV	LTSMLTDPSH	ITAETAKRRL	ARGSPPSLAS	2200
SSASQLSAPS	LKATCTTHHD	SPDADLIEAN	LLWRQEMGGN	ITRVESENKV	2250
VILDSFEPLH	AEGDEREISV	AAEILRKSRK	FPSALPIWAR	PDYNPPLLES	2300
WKDPDYVPPV	VHGCPLPPIK	APPIPPPRRK	RTVVLTESNV	SSALAELATK	2350
TFGSSGSSAV	DSGIATALPD	LASDDGDKGS	DVESYSSMPP	LEGEPGDPDL	2400
SDGSWSTVSE	EASEDVVCCS	MSYTWTGALI	TPCAAEESKL	PINPLSNSLL	2450
RHHNMVYATT	SRSASLRQKK	VTFDRLQVLD	DHYRDVLKEM	KAKASTVKAK	2500
LLSIEEACKL	TPPHSAKSKF	GYGAKDVRNL	SSRAVNHIRS	VWEDLLEDTE	2550
TPIDTTIMAK	SEVFCVQPEK	GGRKPARLIV	FPDLGVRVCE	KMALYDVVST	2600
LPQAVMGSSY	GFQYSPKQRV	EFLVNTWKSK	KCPMGFSYDT	RCFDSTVTES	2650
DIRVEESIYQ	CCDLAPEARQ	AIRSLTERLY	IGGPLTNSKG	QNCGYRRCRA	2700
SGVLTTSCGN	TLTCYLKATA	ACRAAKLQDC	TMLVNGDDLV	VICESAGTQE	2750
DAAALRAFTE	AMTRYSAPPG	DPPQPEYDLE	LITSCSSNVS	VAHDASGKRV	2800
YYLTRDPTTP	LARAAWETAR	HTPINSWLGN	IIMYAPTLWA	RMILMTHFFS	2850
ILLAQEQLEK	ALDCQIYGAC	YSIEPLDLPQ	IIERLHGLSA	FTLHSYSPGE	2900
INRVASCLRK	LGVPPLRTWR	HRARSVRAKL	LSQGGRAATC	GRYLFNWAVR	2950
TKLKLTPIPA	ASQLDLSGWF	VAGYSGGDIY	HSLSRARPRW	FPLCLLLLSV	3000
GVGIYLLPNR					3010

FIG. 7H

SEQUENCE LISTING

<110> Bukh, Jens
Purcell, Robert
Yanagi, Masayuki
Emerson, Suzanne

<120> Infectious cDNA Clone of GB virus B and Uses Thereof

<130> 2026-4308PC

<140> TBA
<141> 2000-06-02

<150> 60/137,694
<151> 1999-06-04

<160> 5

<170> PatentIn Ver. 2.1

<210> 1
<211> 9399
<212> DNA
<213> GBV-B virus

<400> 1
accacaaaca ctccagtttg ttacactccg ctaggaatgc tcctggagca ccccccctag 60
cagggcgtgg gggatttccc ctgcccgtct gcagaagggt ggagccaacc accttagtat 120
gtaggcggcg ggactcatga cgctcgcgtg atgacaagcg ccaagcttga cttggatggc 180
cctgatgggc gttcatgggt tcggtggtgg tggcgcttta ggcagcctcc acgcccacca 240
cctcccagat agagcggcgg cactgtaggg aagaccgggg accggtcact accaaggacg 300
cagacctctt tttgagtatc acgcctccgg aagtagttgg gcaagcccac ctatatgtgt 360
tgggatggtt ggggttagcc atccataccg tactgcctga tagggtcctt gcgaggggat 420
ctgggagtct cgtagaccgt agcacatgcc tgttatttct actcaaacaa gtcctgtacc 480
tgcgcccaga acgcgcaaga acaagcagac gcaggcttca tatcctgtgt ccattaaaac 540
atctgttgaa aggggacaac gagcaaagcg caaagtccag cgcgatgctc ggcctcgtaa 600
ttacaaaatt gctggtatcc atgatggctt gcagacattg gctcaggctg ctttgccagc 660
tcatggttgg ggacgccaag accctcgcca taagtctcgc aatcttggaa tccttctgga 720
ttacccttta gggtggattg gtgatgttac aactcacaca cctctagtag gcccgctggt 780
ggcaggagcg gtcgttcgac cagtctgcca gatagtacgc ttgctggagg atggagtcaa 840
ctgggctact ggttggttcg gtgtccacct ttttgtggta tgtctgctat ctttggcctg 900
tccctgtagt ggggcgcggg tcactgaccc agacacaaat accacaatcc tgaccaattg 960
ctgccagcgt aatcaggtta tctattgttc tccttccact tgcctacacg agcctggttg 1020
tgtgatctgt gcggacgagt gctgggttcc cgccaatccg tacatctcac acccttccaa 1080
ttggactggc acggactcct tcttggctga ccacattgat tttgttatgg gcgctcttgt 1140
gacctgtgac gcccttgaca ttggtgagtt gtgtggtgcg tgtgtattag tcggtgactg 1200
gcttgtcagg cactggctta ttcacataga cctcaatgaa actggtactt gttacctgga 1260

agtgcccact ggaatagatc ctgggttcct agggtttatc gggtggatgg ccggcaaggt 1320
cgaggctgtc atcttcttga ccaaactggc ttcacaagta ccatacgcta ttgcgactat 1380
gtttagcagt gtacactacc tggcggttgg cgctctgatc tactatgcct ctcggggcaa 1440
gtggtatcag ttgctcctag cgcttatgct ttacatagaa gcgacctctg gaaaccccat 1500
cagggtgccc actggatgct caatagctga gttttgctcg cctttgatga taccatgtcc 1560
ttgccactct tatttgagtg agaatgtgtc agaagtcatt tgttacagtc caaagtggac 1620
caggcctatc actctagagt ataacaactc catatcttgg tacccctata caatccctgg 1680
tgcgagggga tgtatggtta aattcaaaaa taacacatgg ggttgctgcc gtattcgcaa 1740
tgtgccatcg tactgcacta tgggcactga tgcagtgtgg aacgacactc gcaacactta 1800
cgaagcatgc ggtgtaacac catggctaac aaccgcatgg cacaacggct cagccctgaa 1860
attggctata ttacaatacc ctgggtctaa agaaatgttt aaacctcata attggatgtc 1920
aggccatttg tattttgagg gatcagatac ccctatagtt tacttttatg accctgtgaa 1980
ttccactctc ctaccaccgg agaggtgggc taggttgccc ggtaccccac ctgtggtacg 2040
tggttcttgg ttacaggttc cgcaagggtt ttacagtgat gtgaaagacc tagccacagg 2100
attgatcacc aaagacaaag cctggaaaaa ttatcaggtc ttatattccg ccacgggtgc 2160
tttgtctctt acgggagtta ccaccaaggc cgtggtgcta attctgttgg ggttgtgtgg 2220
cagcaagtat cttattttag cctacctctg ttacttgtcc ctttgttttg ggcgcgcttc 2280
tggttaccct ttgcgtcctg tgctcccatc ccagtcgtat ctccaagctg gctgggatgt 2340
tttgtctaaa gctcaagtag ctccttttgc tttgattttc ttcatctgtt gctatctccg 2400
ctgcaggcta cgttatgctg ccctttttagg gtttgtgccc atggctgcgg gcttgccccc 2460
aactttcttt gttgcagcag ctgctgccca accagattat gactggtggg tgcgactgct 2520
agtggcaggg ttagttttgt gggccggccg taaccgtggt caccgcatag ctctgcttgt 2580
aggtccttgg cctctggtag cgcttttaac cctcttgcat ttggttacgc ctgcttcagc 2640
ttttgatacc gagataattg gagggctgac aataccacct gtagtagcat tagttgtcat 2700
gtctcgtttt ggcttctttg ctcacttgtt acctcgctgt gctttagtta actcctatct 2760
ttggcaacgt tgggagaatt ggttttggaa cgttacacta agaccggaga ggtttttcct 2820
tgtgctggtt tgtttccccg gtgcgacata tgacgcgctg gtgactttct gtgtgtgtca 2880
cgtagctctt ctatgtttaa catccagtgc agcatcgttc tttgggactg actctagggt 2940
tagggcccat agaatgttgg tgcgtctcgg aaagtgtcat gcttggtatt ctcattatgt 3000
tcttaagttt ttcctcttag tgtttggtga gaatggtgtg tttttctata agcacttgca 3060
tggtgatgtc ttgcctaatg attttgcctc gaaactacca ttgcaagagc catttttccc 3120
ttttgaaggc aaggcaaggg tctataggaa tgaaggaaga cgcttggcgt gtggggacac 3180
ggttgatggt ttgcccgttg ttgcgcgtct cggcgacctt gttttcgcag ggttggctat 3240
gccgccagat gggtgggcca ttaccgcacc ttttacgctg cagtgtctct ctgaacgtgg 3300
cacgctgtca gcgatggcag tggtcatgac tggtatagac ccccgaactt ggactggaac 3360
tatcttcaga ttaggatctc tggccactag ctacatggga tttgtttgtg acaacgtgtt 3420
gtatactgct caccatggca gcaaggggcg ccggttggct catcccacag gctctataca 3480
cccaataacc gttgacgcgg ctaatgacca ggacatctat caaccaccat gtggagctgg 3540
gtcccttact cggtgctctt gcggggagac caaggggtat ctggtaacac gactggggtc 3600
attggttgag gtcaacaaat ccgatgaccc ttattggtgt gtgtgcgggg cccttcccat 3660
ggctgttgcc aagggttctt caggtgcccc gattctgtgc tcctccgggc atgttattgg 3720
gatgttcacc gctgctagaa attctggcgg ttcagtcagt cagattaggg ttaggccgtt 3780
ggtgtgtgct ggataccatc cccagtacac agcacatgcc actcttgata caaaacctac 3840
tgtgcctaac gagtattcag tgcaaatttt aattgccccc actggcagcg gcaagtcaac 3900
caaattacca ctttcttaca tgcaggagaa gtatgaggtc ttggtcctaa atcccagtgt 3960
ggctacaaca gcatcaatgc caaagtacat gcacgcgacg tacggcgtga atccaaattg 4020
ctattttaat ggcaaatgta ccaacacagg ggcttcactt acgtacagca catatggcat 4080
gtacctgacc ggagcatgtt cccggaacta tgatgtaatc atttgtgacg aatgccatgc 4140

taccgatgca accaccgtgt tgggcattgg aaaggtccta accgaagctc catccaaaaa 4200
tgttaggcta gtggttcttg ccacggctac ccccccctgga gtaatcccta caccacatgc 4260
caacataact gagattcaat taaccgatga aggcactatc ccctttcatg gaaaaaagat 4320
taaggaggaa aatctgaaga aagggagaca ccttatcttt gaggctacca aaaaacactg 4380
tgatgagctt gctaacgagt tagctcgaaa gggaataaca gctgtctctt actatagggg 4440
atgtgacatc tcaaaaatcc ctgagggcga ctgtgtagta gttgccactg atgccttgtg 4500
tacagggtac actggtgact ttgattccgt gtatgactgc agcctcatgg tagaaggcac 4560
atgccatgtt gaccttgacc ctactttcac catgggtgtt cgtgtgtgcg gggtttcagc 4620
aatagttaaa ggccagcgta ggggccgcac aggccgtggg agagctggca tatactacta 4680
tgtagacggg agttgtaccc cttcgggtat ggttcctgaa tgcaacattg ttgaagcctt 4740
cgacgcagcc aaggcatggt atggtttgtc atcaacagaa gctcaaacta ttctggacac 4800
ctatcgcacc caacctgggt tacctgcgat aggagcaaat ttggacgagt gggctgatct 4860
cttttctatg gtcaaccccg aaccttcatt tgtcaatact gcaaaaagaa ctgctgacaa 4920
ttatgttttg ttgactgcag cccaactaca actgtgtcat cagtatggct atgctgctcc 4980
caatgacgca ccacggtggc agggagcccg gcttgggaaa aaaccttgtg gggttctgtg 5040
gcgcttggac ggcgctgacg cctgtcctgg cccagagccc agcgaggtga ccagatacca 5100
aatgtgcttc actgaagtca atacttctgg gacagccgca ctcgctgttg gcgttggagt 5160
ggctatggct tatctagcca ttgacacttt tggcgccact tgtgtgcggc gttgctggtc 5220
tattacatca gtccctaccg gtgctactgt cgccccagtg gttgacgaag aagaaatcgt 5280
ggaggagtgt gcatcattca ttcccttgga ggccatggtt gctgcaattg acaagctgaa 5340
gagtacaatc accacaacta gtcctttcac attggaaacc gcccttgaaa aacttaacac 5400
ctttcttggg cctcatgcag ctacaatcct tgctatcata gagtattgct gtggtttagt 5460
cactttacct gacaatccct ttgcatcatg cgtgtttgct ttcattgcgg gtattactac 5520
cccactacct cacaagatca aaatgttcct gtcattattt ggaggcgcaa ttgcgtccaa 5580
gcttacagac gctagaggcg cactggcgtt catgatggcc ggggctgcgg gaacagctct 5640
tggtacatgg acatcggtgg gttttgtctt tgacatgcta ggcggctatg ctgccgcctc 5700
atccactgct tgcttgacat ttaaatgctt gatgggtgag tggcccacta tggatcagct 5760
tgctggttta gtctactccg cgttcaatcc ggccgcagga gttgtgggcg tcttgtcagc 5820
ttgtgcaatg tttgctttga caacagcagg gccagatcac tggcccaaca gacttcttac 5880
tatgcttgct aggagcaaca ctgtatgtaa tgagtacttt attgccactc gtgacatccg 5940
caggaagata ctgggcattc tggaggcatc taccccctgg agtgtcatat cagcttgcat 6000
ccgttggctc cacaccccga cggaggatga ttgcggcctc attgcttggg gtctagagat 6060
ttggcagtat gtgtgcaatt tctttgtgat ttgctttaat gtccttaaag ctggagttca 6120
gagcatggtt aacattcctg gttgtccttt ctacagctgc cagaaggggt acaagggccc 6180
ctggattgga tcaggtatgc tccaagcacg ctgtccatgc ggtgctgaac tcatcttttc 6240
tgttgagaat ggttttgcaa aactttacaa aggacccaga acttgttcaa attactggag 6300
aggggctgtt ccagtcaacg ctaggctgtg tgggtcggct agaccggacc caactgattg 6360
gactagtctt gtcgtcaatt atggcgttag ggactactgt aaatatgaga aaatgggaga 6420
tcacattttt gttacagcag tatcctctcc aaatgtctgt ttcacccagg tgcccccaac 6480
cttgagagct gcagtggccg tggacggcgt acaggttcag tgttatctag gtgagcccaa 6540
aactccttgg acgacatctg cttgctgtta cggtcctgac ggtaagggta aaactgttaa 6600
gcttcccttc cgcgttgacg gtcacacacc tggtgtgcgc atgcaactta atttgcgtga 6660
tgcacttgag acaaatgact gtaattccac aaacaacact cctagtgatg aagccgcagt 6720
gtccgctctt gttttcaaac aggagttgcg gcgtacaaac caattgcttg aggcaatttc 6780
agctggcgtt gacaccacca aactgccagc cccctccatc gaagaggtag tggtaagaaa 6840
gcgccagttc cgggcaagaa ctggttcgct taccttgcct ccccctccga gatccgtccc 6900
aggagtgtca tgtcctgaaa gcctgcaacg aagtgacccg ttagaaggtc cttcaaacct 6960
ccctccttca ccacctgttc tacagttggc catgccgatg cccctgttgg gagcgggtga 7020

gtgtaaccct ttcactgcaa ttggatgtgc aatgaccgaa acaggcggag gccctgatga 7080
tttacccagt taccctccca aaaaggaggt ctctgaatgg tcagacgaaa gttggtcgac 7140
ggctacaacc gcttccagct acgttactgg ccccccgtac cctaagatac ggggaaagga 7200
ttccactcag tcagcccccg ccaaacggcc tacaaaaaag aagttgggaa agagtgagtt 7260
ttcgtgcagc atgagctaca cctggaccga cgtgattagc ttcaaaactg cttctaaagt 7320
tctgtctgca actcgggcca tcactagtgg tttcctcaaa caaagatcat tggtgtatgt 7380
gactgagccg cgggatgcgg agcttagaaa acaaaaagtc actattaata gacaacctct 7440
gttcccccca tcataccaca agcaagtgag attggctaag gaaaaagctt caaaagttgt 7500
cggtgtcatg tgggactatg atgaagtagc agctcacacg ccctctaagt ctgctaagtc 7560
ccacatcact ggccttcggg gcactgatgt tcgttctgga gcagcccgca aggctgttct 7620
ggacttgcag aagtgtgtcg aggcaggtga gataccgagt cattatcggc aaactgtgat 7680
agttccaaag gaggaggtct tcgtgaagac cccccagaaa ccaacaaaga aacccccaag 7740
gcttatctcg tacccccacc ttgaaatgag atgtgttgag aagatgtact acggtcaggt 7800
tgctcctgac gtagttaaag ctgtcatggg agatgcgtac gggtttgtag atccacgtac 7860
ccgtgtcaag cgtctgttgt cgatgtggtc acccgatgca gtcggagcca catgcgatac 7920
agtgtgtttt gacagtacca tcacacccga ggatatcatg gtggagacag acatctactc 7980
agcagctaaa ctcagtgacc aacaccgagc tggcattcac accattgcga ggcagttata 8040
cgctggagga ccgatgatcg cttatgatgg ccgagagatc ggatatcgta ggtgtaggtc 8100
ttccggcgtc tatactacct caagttccaa cagtttgacc tgctggctga aggtaaatgc 8160
tgcagccgaa caggctggca tgaagaaccc tcgcttcctt atttgcggcg atgattgcac 8220
cgtaatttgg aagagcgccg gagcagatgc agacaaacaa gcaatgcgtg tctttgctag 8280
ctggatgaag gtgatgggtg caccacaaga ttgtgtgcct caacccaaat acagtttgga 8340
agaattaaca tcatgctcat caaatgttac ctctggaatt accaaaagtg gcaagcctta 8400
ctactttctt acaagagatc ctcgtatccc ccttggcagg tgctctgccg agggtctggg 8460
atacaacccc agtgctgcgt ggattgggta tctaatacat cactacccat gtttgtgggt 8520
tagccgtgtg ttggctgtcc atttcatgga gcagatgctc tttgaggaca aacttcccga 8580
gactgtgacc tttgactggt atgggaaaaa ttatacggtg cctgtagaag atctgcccag 8640
catcattgct ggtgtgcacg gtattgaggc tttctcggtg gtgcgctaca ccaacgctga 8700
gatcctcaga gtttcccaat cactaacaga catgaccatg ccccccctgc gagcctggcg 8760
aaagaaagcc agggcggtcc tcgccagcgc caagaggcgt ggcggagcac acgcaaaatt 8820
ggctcgcttc cttctctggc atgctacatc tagacctcta ccagatttgg ataagacgag 8880
cgtggctcgg tacaccactt tcaattattg tgatgtttac tccccggagg gggatgtgtt 8940
tattacacca cagagaagat tgcagaagtt ccttgtgaag tatttggctg tcattgtttt 9000
tgccctaggg ctcattgctg ttggattagc catcagctga acccccaaat tcaaaattaa 9060
ctaacagttt tttttttttt tttttttttt agggcagcgg caacagggga gaccccgggc 9120
ttaacgaccc cgccgatgtg agtttggcga ccatggtgga tcagaaccgt ttcgggtgaa 9180
gccatggtct gaaggggatg acgtcccttc tggctcatcc acaaaaaccg tctcgggtgg 9240
gtgaggagtc ctggctgtgt gggaagcagt cagtataatt cccgtcgtgt gtggtgacgc 9300
ctcacgacgt atttgtccgc tgtgcagagc gtagtaccaa gggctgcacc ccggtttttg 9360
ttccaagcgg agggcaaccc ccgcttggaa ttaaaaact 9399

<210> 2
<211> 2864
<212> PRT
<213> GBV-B virus

<400> 2

```
Met Pro Val Ile Ser Thr Gln Thr Ser Pro Val Pro Ala Pro Arg Thr
 1               5                  10                  15

Arg Lys Asn Lys Gln Thr Gln Ala Ser Tyr Pro Val Ser Ile Lys Thr
            20                  25                  30

Ser Val Glu Arg Gly Gln Arg Ala Lys Arg Lys Val Gln Arg Asp Ala
        35                  40                  45

Arg Pro Arg Asn Tyr Lys Ile Ala Gly Ile His Asp Gly Leu Gln Thr
    50                  55                  60

Leu Ala Gln Ala Ala Leu Pro Ala His Gly Trp Gly Arg Gln Asp Pro
65                  70                  75                  80

Arg His Lys Ser Arg Asn Leu Gly Ile Leu Leu Asp Tyr Pro Leu Gly
                85                  90                  95

Trp Ile Gly Asp Val Thr Thr His Thr Pro Leu Val Gly Pro Leu Val
            100                 105                 110

Ala Gly Ala Val Val Arg Pro Val Cys Gln Ile Val Arg Leu Leu Glu
        115                 120                 125

Asp Gly Val Asn Trp Ala Thr Gly Trp Phe Gly Val His Leu Phe Val
    130                 135                 140

Val Cys Leu Leu Ser Leu Ala Cys Pro Cys Ser Gly Ala Arg Val Thr
145                 150                 155                 160

Asp Pro Asp Thr Asn Thr Thr Ile Leu Thr Asn Cys Cys Gln Arg Asn
                165                 170                 175

Gln Val Ile Tyr Cys Ser Pro Ser Thr Cys Leu His Glu Pro Gly Cys
            180                 185                 190

Val Ile Cys Ala Asp Glu Cys Trp Val Pro Ala Asn Pro Tyr Ile Ser
        195                 200                 205

His Pro Ser Asn Trp Thr Gly Thr Asp Ser Phe Leu Ala Asp His Ile
    210                 215                 220

Asp Phe Val Met Gly Ala Leu Val Thr Cys Asp Ala Leu Asp Ile Gly
225                 230                 235                 240

Glu Leu Cys Gly Ala Cys Val Leu Val Gly Asp Trp Leu Val Arg His
                245                 250                 255
```

```
Trp Leu Ile His Ile Asp Leu Asn Glu Thr Gly Thr Cys Tyr Leu Glu
            260                 265                 270

Val Pro Thr Gly Ile Asp Pro Gly Phe Leu Gly Phe Ile Gly Trp Met
        275                 280                 285

Ala Gly Lys Val Glu Ala Val Ile Phe Leu Thr Lys Leu Ala Ser Gln
    290                 295                 300

Val Pro Tyr Ala Ile Ala Thr Met Phe Ser Ser Val His Tyr Leu Ala
305                 310                 315                 320

Val Gly Ala Leu Ile Tyr Tyr Ala Ser Arg Gly Lys Trp Tyr Gln Leu
                325                 330                 335

Leu Leu Ala Leu Met Leu Tyr Ile Glu Ala Thr Ser Gly Asn Pro Ile
            340                 345                 350

Arg Val Pro Thr Gly Cys Ser Ile Ala Glu Phe Cys Ser Pro Leu Met
        355                 360                 365

Ile Pro Cys Pro Cys His Ser Tyr Leu Ser Glu Asn Val Ser Glu Val
    370                 375                 380

Ile Cys Tyr Ser Pro Lys Trp Thr Arg Pro Ile Thr Leu Glu Tyr Asn
385                 390                 395                 400

Asn Ser Ile Ser Trp Tyr Pro Tyr Thr Ile Pro Gly Ala Arg Gly Cys
                405                 410                 415

Met Val Lys Phe Lys Asn Asn Thr Trp Gly Cys Cys Arg Ile Arg Asn
            420                 425                 430

Val Pro Ser Tyr Cys Thr Met Gly Thr Asp Ala Val Trp Asn Asp Thr
        435                 440                 445

Arg Asn Thr Tyr Glu Ala Cys Gly Val Thr Pro Trp Leu Thr Thr Ala
    450                 455                 460

Trp His Asn Gly Ser Ala Leu Lys Leu Ala Ile Leu Gln Tyr Pro Gly
465                 470                 475                 480

Ser Lys Glu Met Phe Lys Pro His Asn Trp Met Ser Gly His Leu Tyr
                485                 490                 495

Phe Glu Gly Ser Asp Thr Pro Ile Val Tyr Phe Tyr Asp Pro Val Asn
            500                 505                 510
```

```
Ser Thr Leu Leu Pro Pro Glu Arg Trp Ala Arg Leu Pro Gly Thr Pro
        515                 520                 525

Pro Val Val Arg Gly Ser Trp Leu Gln Val Pro Gln Gly Phe Tyr Ser
    530                 535                 540

Asp Val Lys Asp Leu Ala Thr Gly Leu Ile Thr Lys Asp Lys Ala Trp
545                 550                 555                 560

Lys Asn Tyr Gln Val Leu Tyr Ser Ala Thr Gly Ala Leu Ser Leu Thr
                565                 570                 575

Gly Val Thr Thr Lys Ala Val Val Leu Ile Leu Leu Gly Leu Cys Gly
            580                 585                 590

Ser Lys Tyr Leu Ile Leu Ala Tyr Leu Cys Tyr Leu Ser Leu Cys Phe
        595                 600                 605

Gly Arg Ala Ser Gly Tyr Pro Leu Arg Pro Val Leu Pro Ser Gln Ser
    610                 615                 620

Tyr Leu Gln Ala Gly Trp Asp Val Leu Ser Lys Ala Gln Val Ala Pro
625                 630                 635                 640

Phe Ala Leu Ile Phe Phe Ile Cys Cys Tyr Leu Arg Cys Arg Leu Arg
                645                 650                 655

Tyr Ala Ala Leu Leu Gly Phe Val Pro Met Ala Ala Gly Leu Pro Leu
            660                 665                 670

Thr Phe Phe Val Ala Ala Ala Ala Ala Gln Pro Asp Tyr Asp Trp Trp
        675                 680                 685

Val Arg Leu Leu Val Ala Gly Leu Val Leu Trp Ala Gly Arg Asn Arg
    690                 695                 700

Gly His Arg Ile Ala Leu Leu Val Gly Pro Trp Pro Leu Val Ala Leu
705                 710                 715                 720

Leu Thr Leu Leu His Leu Val Thr Pro Ala Ser Ala Phe Asp Thr Glu
                725                 730                 735

Ile Ile Gly Gly Leu Thr Ile Pro Pro Val Val Ala Leu Val Val Met
            740                 745                 750

Ser Arg Phe Gly Phe Phe Ala His Leu Leu Pro Arg Cys Ala Leu Val
        755                 760                 765
```

```
Asn Ser Tyr Leu Trp Gln Arg Trp Glu Asn Trp Phe Trp Asn Val Thr
    770                 775                 780

Leu Arg Pro Glu Arg Phe Phe Leu Val Leu Val Cys Phe Pro Gly Ala
785                 790                 795                 800

Thr Tyr Asp Ala Leu Val Thr Phe Cys Val Cys His Val Ala Leu Leu
                805                 810                 815

Cys Leu Thr Ser Ser Ala Ala Ser Phe Phe Gly Thr Asp Ser Arg Val
            820                 825                 830

Arg Ala His Arg Met Leu Val Arg Leu Gly Lys Cys His Ala Trp Tyr
        835                 840                 845

Ser His Tyr Val Leu Lys Phe Phe Leu Leu Val Phe Gly Glu Asn Gly
    850                 855                 860

Val Phe Phe Tyr Lys His Leu His Gly Asp Val Leu Pro Asn Asp Phe
865                 870                 875                 880

Ala Ser Lys Leu Pro Leu Gln Glu Pro Phe Phe Pro Phe Glu Gly Lys
                885                 890                 895

Ala Arg Val Tyr Arg Asn Glu Gly Arg Arg Leu Ala Cys Gly Asp Thr
            900                 905                 910

Val Asp Gly Leu Pro Val Val Ala Arg Leu Gly Asp Leu Val Phe Ala
        915                 920                 925

Gly Leu Ala Met Pro Pro Asp Gly Trp Ala Ile Thr Ala Pro Phe Thr
    930                 935                 940

Leu Gln Cys Leu Ser Glu Arg Gly Thr Leu Ser Ala Met Ala Val Val
945                 950                 955                 960

Met Thr Gly Ile Asp Pro Arg Thr Trp Thr Gly Thr Ile Phe Arg Leu
                965                 970                 975

Gly Ser Leu Ala Thr Ser Tyr Met Gly Phe Val Cys Asp Asn Val Leu
            980                 985                 990

Tyr Thr Ala His His Gly Ser Lys Gly Arg Arg Leu Ala His Pro Thr
        995                1000                1005

Gly Ser Ile His Pro Ile Thr Val Asp Ala Ala Asn Asp Gln Asp Ile
   1010                1015                1020
```

```
Tyr Gln Pro Pro Cys Gly Ala Gly Ser Leu Thr Arg Cys Ser Cys Gly
1025                1030                1035                1040

Glu Thr Lys Gly Tyr Leu Val Thr Arg Leu Gly Ser Leu Val Glu Val
                1045                1050                1055

Asn Lys Ser Asp Asp Pro Tyr Trp Cys Val Cys Gly Ala Leu Pro Met
            1060                1065                1070

Ala Val Ala Lys Gly Ser Ser Gly Ala Pro Ile Leu Cys Ser Ser Gly
        1075                1080                1085

His Val Ile Gly Met Phe Thr Ala Ala Arg Asn Ser Gly Gly Ser Val
    1090                1095                1100

Ser Gln Ile Arg Val Arg Pro Leu Val Cys Ala Gly Tyr His Pro Gln
1105                1110                1115                1120

Tyr Thr Ala His Ala Thr Leu Asp Thr Lys Pro Thr Val Pro Asn Glu
                1125                1130                1135

Tyr Ser Val Gln Ile Leu Ile Ala Pro Thr Gly Ser Gly Lys Ser Thr
            1140                1145                1150

Lys Leu Pro Leu Ser Tyr Met Gln Glu Lys Tyr Glu Val Leu Val Leu
        1155                1160                1165

Asn Pro Ser Val Ala Thr Thr Ala Ser Met Pro Lys Tyr Met His Ala
    1170                1175                1180

Thr Tyr Gly Val Asn Pro Asn Cys Tyr Phe Asn Gly Lys Cys Thr Asn
1185                1190                1195                1200

Thr Gly Ala Ser Leu Thr Tyr Ser Thr Tyr Gly Met Tyr Leu Thr Gly
                1205                1210                1215

Ala Cys Ser Arg Asn Tyr Asp Val Ile Ile Cys Asp Glu Cys His Ala
            1220                1225                1230

Thr Asp Ala Thr Thr Val Leu Gly Ile Gly Lys Val Leu Thr Glu Ala
        1235                1240                1245

Pro Ser Lys Asn Val Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
    1250                1255                1260

Gly Val Ile Pro Thr Pro His Ala Asn Ile Thr Glu Ile Gln Leu Thr
1265                1270                1275                1280
```

```
Asp Glu Gly Thr Ile Pro Phe His Gly Lys Lys Ile Lys Glu Glu Asn
                1285                1290                1295

Leu Lys Lys Gly Arg His Leu Ile Phe Glu Ala Thr Lys Lys His Cys
            1300                1305                1310

Asp Glu Leu Ala Asn Glu Leu Ala Arg Lys Gly Ile Thr Ala Val Ser
        1315                1320                1325

Tyr Tyr Arg Gly Cys Asp Ile Ser Lys Ile Pro Glu Gly Asp Cys Val
    1330                1335                1340

Val Val Ala Thr Asp Ala Leu Cys Thr Gly Tyr Thr Gly Asp Phe Asp
1345                1350                1355                1360

Ser Val Tyr Asp Cys Ser Leu Met Val Glu Gly Thr Cys His Val Asp
                1365                1370                1375

Leu Asp Pro Thr Phe Thr Met Gly Val Arg Val Cys Gly Val Ser Ala
            1380                1385                1390

Ile Val Lys Gly Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Ala Gly
        1395                1400                1405

Ile Tyr Tyr Tyr Val Asp Gly Ser Cys Thr Pro Ser Gly Met Val Pro
    1410                1415                1420

Glu Cys Asn Ile Val Glu Ala Phe Asp Ala Ala Lys Ala Trp Tyr Gly
1425                1430                1435                1440

Leu Ser Ser Thr Glu Ala Gln Thr Ile Leu Asp Thr Tyr Arg Thr Gln
                1445                1450                1455

Pro Gly Leu Pro Ala Ile Gly Ala Asn Leu Asp Glu Trp Ala Asp Leu
            1460                1465                1470

Phe Ser Met Val Asn Pro Glu Pro Ser Phe Val Asn Thr Ala Lys Arg
        1475                1480                1485

Thr Ala Asp Asn Tyr Val Leu Leu Thr Ala Ala Gln Leu Gln Leu Cys
    1490                1495                1500

His Gln Tyr Gly Tyr Ala Ala Pro Asn Asp Ala Pro Arg Trp Gln Gly
1505                1510                1515                1520

Ala Arg Leu Gly Lys Lys Pro Cys Gly Val Leu Trp Arg Leu Asp Gly
                1525                1530                1535
```

```
Ala Asp Ala Cys Pro Gly Pro Glu Pro Ser Glu Val Thr Arg Tyr Gln
          1540                1545                1550

Met Cys Phe Thr Glu Val Asn Thr Ser Gly Thr Ala Ala Leu Ala Val
      1555                1560                1565

Gly Val Gly Val Ala Met Ala Tyr Leu Ala Ile Asp Thr Phe Gly Ala
  1570                1575                1580

Thr Cys Val Arg Arg Cys Trp Ser Ile Thr Ser Val Pro Thr Gly Ala
1585                1590                1595                1600

Thr Val Ala Pro Val Val Asp Glu Glu Glu Ile Val Glu Glu Cys Ala
              1605                1610                1615

Ser Phe Ile Pro Leu Glu Ala Met Val Ala Ala Ile Asp Lys Leu Lys
          1620                1625                1630

Ser Thr Ile Thr Thr Thr Ser Pro Phe Thr Leu Glu Thr Ala Leu Glu
      1635                1640                1645

Lys Leu Asn Thr Phe Leu Gly Pro His Ala Ala Thr Ile Leu Ala Ile
  1650                1655                1660

Ile Glu Tyr Cys Cys Gly Leu Val Thr Leu Pro Asp Asn Pro Phe Ala
1665                1670                1675                1680

Ser Cys Val Phe Ala Phe Ile Ala Gly Ile Thr Thr Pro Leu Pro His
              1685                1690                1695

Lys Ile Lys Met Phe Leu Ser Leu Phe Gly Gly Ala Ile Ala Ser Lys
          1700                1705                1710

Leu Thr Asp Ala Arg Gly Ala Leu Ala Phe Met Met Ala Gly Ala Ala
      1715                1720                1725

Gly Thr Ala Leu Gly Thr Trp Thr Ser Val Gly Phe Val Phe Asp Met
  1730                1735                1740

Leu Gly Gly Tyr Ala Ala Ala Ser Ser Thr Ala Cys Leu Thr Phe Lys
1745                1750                1755                1760

Cys Leu Met Gly Glu Trp Pro Thr Met Asp Gln Leu Ala Gly Leu Val
              1765                1770                1775

Tyr Ser Ala Phe Asn Pro Ala Ala Gly Val Val Gly Val Leu Ser Ala
          1780                1785                1790
```

```
Cys Ala Met Phe Ala Leu Thr Thr Ala Gly Pro Asp His Trp Pro Asn
       1795                1800                1805

Arg Leu Leu Thr Met Leu Ala Arg Ser Asn Thr Val Cys Asn Glu Tyr
   1810                1815                1820

Phe Ile Ala Thr Arg Asp Ile Arg Arg Lys Ile Leu Gly Ile Leu Glu
1825                1830                1835                1840

Ala Ser Thr Pro Trp Ser Val Ile Ser Ala Cys Ile Arg Trp Leu His
               1845                1850                1855

Thr Pro Thr Glu Asp Asp Cys Gly Leu Ile Ala Trp Gly Leu Glu Ile
           1860                1865                1870

Trp Gln Tyr Val Cys Asn Phe Phe Val Ile Cys Phe Asn Val Leu Lys
       1875                1880                1885

Ala Gly Val Gln Ser Met Val Asn Ile Pro Gly Cys Pro Phe Tyr Ser
   1890                1895                1900

Cys Gln Lys Gly Tyr Lys Gly Pro Trp Ile Gly Ser Gly Met Leu Gln
1905                1910                1915                1920

Ala Arg Cys Pro Cys Gly Ala Glu Leu Ile Phe Ser Val Glu Asn Gly
               1925                1930                1935

Phe Ala Lys Leu Tyr Lys Gly Pro Arg Thr Cys Ser Asn Tyr Trp Arg
           1940                1945                1950

Gly Ala Val Pro Val Asn Ala Arg Leu Cys Gly Ser Ala Arg Pro Asp
       1955                1960                1965

Pro Thr Asp Trp Thr Ser Leu Val Val Asn Tyr Gly Val Arg Asp Tyr
   1970                1975                1980

Cys Lys Tyr Glu Lys Met Gly Asp His Ile Phe Val Thr Ala Val Ser
1985                1990                1995                2000

Ser Pro Asn Val Cys Phe Thr Gln Val Pro Pro Thr Leu Arg Ala Ala
               2005                2010                2015

Val Ala Val Asp Gly Val Gln Val Gln Cys Tyr Leu Gly Glu Pro Lys
           2020                2025                2030

Thr Pro Trp Thr Thr Ser Ala Cys Cys Tyr Gly Pro Asp Gly Lys Gly
       2035                2040                2045
```

Lys Thr Val Lys Leu Pro Phe Arg Val Asp Gly His Thr Pro Gly Val
2050 2055 2060

Arg Met Gln Leu Asn Leu Arg Asp Ala Leu Glu Thr Asn Asp Cys Asn
2065 2070 2075 2080

Ser Thr Asn Asn Thr Pro Ser Asp Glu Ala Ala Val Ser Ala Leu Val
2085 2090 2095

Phe Lys Gln Glu Leu Arg Arg Thr Asn Gln Leu Leu Glu Ala Ile Ser
2100 2105 2110

Ala Gly Val Asp Thr Thr Lys Leu Pro Ala Pro Ser Ile Glu Glu Val
2115 2120 2125

Val Val Arg Lys Arg Gln Phe Arg Ala Arg Thr Gly Ser Leu Thr Leu
2130 2135 2140

Pro Pro Pro Pro Arg Ser Val Pro Gly Val Ser Cys Pro Glu Ser Leu
2145 2150 2155 2160

Gln Arg Ser Asp Pro Leu Glu Gly Pro Ser Asn Leu Pro Pro Ser Pro
2165 2170 2175

Pro Val Leu Gln Leu Ala Met Pro Met Pro Leu Leu Gly Ala Gly Glu
2180 2185 2190

Cys Asn Pro Phe Thr Ala Ile Gly Cys Ala Met Thr Glu Thr Gly Gly
2195 2200 2205

Gly Pro Asp Asp Leu Pro Ser Tyr Pro Pro Lys Lys Glu Val Ser Glu
2210 2215 2220

Trp Ser Asp Glu Ser Trp Ser Thr Ala Thr Thr Ala Ser Ser Tyr Val
2225 2230 2235 2240

Thr Gly Pro Pro Tyr Pro Lys Ile Arg Gly Lys Asp Ser Thr Gln Ser
2245 2250 2255

Ala Pro Ala Lys Arg Pro Thr Lys Lys Lys Leu Gly Lys Ser Glu Phe
2260 2265 2270

Ser Cys Ser Met Ser Tyr Thr Trp Thr Asp Val Ile Ser Phe Lys Thr
2275 2280 2285

Ala Ser Lys Val Leu Ser Ala Thr Arg Ala Ile Thr Ser Gly Phe Leu
2290 2295 2300

Lys Gln Arg Ser Leu Val Tyr Val Thr Glu Pro Arg Asp Ala Glu Leu
2305 2310 2315 2320

Arg Lys Gln Lys Val Thr Ile Asn Arg Gln Pro Leu Phe Pro Pro Ser
2325 2330 2335

Tyr His Lys Gln Val Arg Leu Ala Lys Glu Lys Ala Ser Lys Val Val
2340 2345 2350

Gly Val Met Trp Asp Tyr Asp Glu Val Ala Ala His Thr Pro Ser Lys
2355 2360 2365

Ser Ala Lys Ser His Ile Thr Gly Leu Arg Gly Thr Asp Val Arg Ser
2370 2375 2380

Gly Ala Ala Arg Lys Ala Val Leu Asp Leu Gln Lys Cys Val Glu Ala
2385 2390 2395 2400

Gly Glu Ile Pro Ser His Tyr Arg Gln Thr Val Ile Val Pro Lys Glu
2405 2410 2415

Glu Val Phe Val Lys Thr Pro Gln Lys Pro Thr Lys Lys Pro Pro Arg
2420 2425 2430

Leu Ile Ser Tyr Pro His Leu Glu Met Arg Cys Val Glu Lys Met Tyr
2435 2440 2445

Tyr Gly Gln Val Ala Pro Asp Val Val Lys Ala Val Met Gly Asp Ala
2450 2455 2460

Tyr Gly Phe Val Asp Pro Arg Thr Arg Val Lys Arg Leu Leu Ser Met
2465 2470 2475 2480

Trp Ser Pro Asp Ala Val Gly Ala Thr Cys Asp Thr Val Cys Phe Asp
2485 2490 2495

Ser Thr Ile Thr Pro Glu Asp Ile Met Val Glu Thr Asp Ile Tyr Ser
2500 2505 2510

Ala Ala Lys Leu Ser Asp Gln His Arg Ala Gly Ile His Thr Ile Ala
2515 2520 2525

Arg Gln Leu Tyr Ala Gly Gly Pro Met Ile Ala Tyr Asp Gly Arg Glu
2530 2535 2540

Ile Gly Tyr Arg Arg Cys Arg Ser Ser Gly Val Tyr Thr Thr Ser Ser
2545 2550 2555 2560

Ser Asn Ser Leu Thr Cys Trp Leu Lys Val Asn Ala Ala Ala Glu Gln
2565 2570 2575

Ala Gly Met Lys Asn Pro Arg Phe Leu Ile Cys Gly Asp Asp Cys Thr
2580 2585 2590

Val Ile Trp Lys Ser Ala Gly Ala Asp Ala Asp Lys Gln Ala Met Arg
2595 2600 2605

Val Phe Ala Ser Trp Met Lys Val Met Gly Ala Pro Gln Asp Cys Val
2610 2615 2620

Pro Gln Pro Lys Tyr Ser Leu Glu Glu Leu Thr Ser Cys Ser Ser Asn
2625 2630 2635 2640

Val Thr Ser Gly Ile Thr Lys Ser Gly Lys Pro Tyr Tyr Phe Leu Thr
2645 2650 2655

Arg Asp Pro Arg Ile Pro Leu Gly Arg Cys Ser Ala Glu Gly Leu Gly
2660 2665 2670

Tyr Asn Pro Ser Ala Ala Trp Ile Gly Tyr Leu Ile His His Tyr Pro
2675 2680 2685

Cys Leu Trp Val Ser Arg Val Leu Ala Val His Phe Met Glu Gln Met
2690 2695 2700

Leu Phe Glu Asp Lys Leu Pro Glu Thr Val Thr Phe Asp Trp Tyr Gly
2705 2710 2715 2720

Lys Asn Tyr Thr Val Pro Val Glu Asp Leu Pro Ser Ile Ile Ala Gly
2725 2730 2735

Val His Gly Ile Glu Ala Phe Ser Val Val Arg Tyr Thr Asn Ala Glu
2740 2745 2750

Ile Leu Arg Val Ser Gln Ser Leu Thr Asp Met Thr Met Pro Pro Leu
2755 2760 2765

Arg Ala Trp Arg Lys Lys Ala Arg Ala Val Leu Ala Ser Ala Lys Arg
2770 2775 2780

Arg Gly Gly Ala His Ala Lys Leu Ala Arg Phe Leu Leu Trp His Ala
2785 2790 2795 2800

Thr Ser Arg Pro Leu Pro Asp Leu Asp Lys Thr Ser Val Ala Arg Tyr
2805 2810 2815

Thr Thr Phe Asn Tyr Cys Asp Val Tyr Ser Pro Glu Gly Asp Val Phe
2820 2825 2830

Ile Thr Pro Gln Arg Arg Leu Gln Lys Phe Leu Val Lys Tyr Leu Ala
2835 2840 2845

Val Ile Val Phe Ala Leu Gly Leu Ile Ala Val Gly Leu Ala Ile Ser
2850 2855 2860

<210> 3
<211> 9139
<212> DNA
<213> GBV-B virus

<400> 3
accacaaaca ctccagtttg ttacactccg ctaggaatgc tcctggagca ccccccctag 60
cagggcgtgg gggatttccc ctgcccgtct gcagaagggt ggagccaacc accttagtat 120
gtaggcggcg ggactcatga cgctcgcgtg atgacaagcg ccaagcttga cttggatggc 180
cctgatgggc gttcatgggt tcggtggtgg tggcgcttta ggcagcctcc acgcccacca 240
cctcccagat agagcggcgg cactgtaggg aagaccgggg accggtcact accaaggacg 300
cagacctctt tttgagtatc acgcctccgg aagtagttgg gcaagcccac ctatatgtgt 360
tgggatggtt ggggttagcc atccataccg tactgcctga tagggtcctt gcgaggggat 420
ctgggagtct cgtagaccgt agcacatgcc tgttatttct actcaaacaa gtcctgtacc 480
tgcgcccaga acgcgcaaga acaagcagac gcaggcttca tatcctgtgt ccattaaaac 540
atctgttgaa aggggacaac gagcaaagcg caaagtccag cgcgatgctc ggcctcgtaa 600
ttacaaaatt gctggtatcc atgatggctt gcagacattg gctcaggctg ctttgccagc 660
tcatggttgg ggacgccaag accctcgcca taagtctcgc aatcttggaa tccttctgga 720
ttacccttg gggtggattg gtgatgttac aactcacaca cctctagtag gcccgctggt 780
ggcaggagcg gtcgttcgac cagtctgcca gatagtacgc ttgctggagg atggagtcaa 840
ctgggctact ggttggttcg gtgtccacct ttttgtggta tgtctgctat ctttggcctg 900
tccctgtagt ggggcgcggg tcactgaccc agacacaaat accacaatcc tgaccaattg 960
ctgccagcgt aatcaggtta tctattgttc tccttccact tgcctacacg agcctggttg 1020
tgtgatctgt gcggacgagt gctgggttcc cgccaatccg tacatctcac acccttccaa 1080
ttggactggc acggactcct tcttggctga ccacattgat tttgttatgg gcgctcttgt 1140
gacctgtgac gcccttgaca ttggtgagtt gtgtggtgcg tgtgtattag tcggtgactg 1200
gcttgtcagg cactggctta ttcacataga cctcaatgaa actggtactt gttacctgga 1260
agtgcccact ggaatagatc ctgggttcct agggtttatc gggtggatgg ccggcaaggt 1320
cgaggctgtc atcttcttga ccaaactggc ttcacaagta ccatacgcta ttgcgactat 1380
gtttagcagt gtacactacc tggcggttgg cgctctgatc tactatgcct ctcggggcaa 1440
gtggtatcag ttgctcctag cgcttatgct ttacatagaa gcgacctctg gaaaccccat 1500
cagggtgccc actggatgct caatagctga gttttgctcg cctttgatga taccatgtcc 1560
ttgccactct tatttgagtg agaatgtgtc agaagtcatt tgttacagtc caaagtggac 1620
caggcctatc actctagagt ataacaactc catatcttgg taccctata caatccctgg 1680
tgcgagggga tgtatggtta aattcaaaaa taacacatgg ggttgctgcc gtattcgcaa 1740

tgtgccatcg tactgcacta tgggcactga tgcagtgtgg aacgacactc gcaacactta 1800
cgaagcatgc ggtgtaacac catggctaac aaccgcatgg cacaacggct cagccctgaa 1860
attggctata ttacaatacc ctgggtctaa agaaatgttt aaacctcata attggatgtc 1920
aggccatttg tattttgagg gatcagatac ccctatagtt tacttttatg accctgtgaa 1980
ttccactctc ctaccaccgg agaggtgggc taggttgccc ggtaccccac ctgtggtacg 2040
tggttcttgg ttacaggttc cgcaagggtt ttacagtgat gtgaaagacc tagccacagg 2100
attgatcacc aaagacaaag cctggaaaaa ttatcaggtc ttatattccg ccacgggtgc 2160
tttgtctctt acgggagtta ccaccaaggc cgtggtgcta attctgttgg ggttgtgtgg 2220
cagcaagtat cttattttag cctacctctg ttacttgtcc ctttgttttg ggcgcgcttc 2280
tggttaccct ttgcgtcctg tgctcccatc ccagtcgtat ctccaagctg gctgggatgt 2340
tttgtctaaa gctcaagtag ctccttttgc tttgattttc ttcatctgtt gctatctccg 2400
ctgcaggcta cgttatgctg ccctttttagg gtttgtgccc atggctgcgg gcttgcccct 2460
aactttcttt gttgcagcag ctgctgccca accagattat gactggtggg tgcgactgct 2520
agtggcaggg ttagttttgt gggccggccg taaccgtggt caccgcatag ctctgcttgt 2580
aggtccttgg cctctggtag cgcttttaac cctcttgcat ttggttacgc ctgcttcagc 2640
ttttgatacc gagataattg gagggctgac aataccacct gtagtagcat tagttgtcat 2700
gtctcgtttt ggcttctttg ctcacttgtt acctcgctgt gctttagtta actcctatct 2760
ttggcaacgt tgggagaatt ggttttggaa cgttacacta agaccggaga ggtttttcct 2820
tgtgctggtt tgtttccccg gtgcgacata tgacgcgctg gtgactttct gtgtgtgtca 2880
cgtagctctt ctatgtttaa catccagtgc agcatcgttc tttgggactg actctagggt 2940
tagggcccat agaatgttgg tgcgtctcgg aaagtgtcat gcttggtatt ctcattatgt 3000
tcttaagttt ttcctcttag tgtttggtga gaatggtgtg tttttctata agcacttgca 3060
tggtgatgtc ttgcctaatg attttgcctc gaaactacca ttgcaagagc catttttccc 3120
ttttgaaggc aaggcaaggg tctataggaa tgaaggaaga cgcttggcgt gtggggacac 3180
ggttgatggt ttgcccgttg ttgcgcgtct cggcgacctt gttttcgcag ggttggctat 3240
gccgccagat gggtgggcca ttaccgcacc ttttacgctg cagtgtctct ctgaacgtgg 3300
cacgctgtca gcgatggcag tggtcatgac tggtatagac ccccgaactt ggactggaac 3360
tatcttcaga ttaggatctc tggccactag ctacatggga tttgtttgtg acaacgtgtt 3420
gtatactgct caccatggca gcaaggggcg ccggttggct catcccacag gctctataca 3480
cccaataacc gttgacgcgg ctaatgacca ggacatctat caaccaccat gtggagctgg 3540
gtcccttact cggtgctctt gcggggagac caaggggtat ctggtaacac gactggggtc 3600
attggttgag gtcaacaaat ccgatgaccc ttattggtgt gtgtgcgggg cccttcccat 3660
ggctgttgcc aagggttctt caggtgcccc gattctgtgc tcctccgggc atgttattgg 3720
gatgttcacc gctgctagaa attctggcgg ttcagtcagt cagattaggg ttaggccgtt 3780
ggtgtgtgct ggataccatc cccagtacac agcacatgcc actcttgata caaaacctac 3840
tgtgcctaac gagtattcag tgcaaatttt aattgccccc actggcagcg gcaagtcaac 3900
caaattacca ctttcttaca tgcaggagaa gtatgaggtc ttggtcctaa atcccagtgt 3960
ggctacaaca gcatcaatgc caaagtacat gcacgcgacg tacggcgtga atccaaattg 4020
ctattttaat ggcaaatgta ccaacacagg ggcttcactt acgtacagca catatggcat 4080
gtacctgacc ggagcatgtt cccggaacta tgatgtaatc atttgtgacg aatgccatgc 4140
taccgatgca accaccgtgt tgggcattgg aaaggtccta accgaagctc catccaaaaa 4200
tgttaggcta gtggttcttg ccacggctac ccccccctgga gtaatcccta caccacatgc 4260
caacataact gagattcaat taaccgatga aggcactatc ccctttcatg gaaaaaagat 4320
taaggaggaa aatctgaaga aagggagaca ccttatcttt gaggctacca aaaaacactg 4380
tgatgagctt gctaacgagt tagctcgaaa gggaataaca gctgtctctt actatagggg 4440
atgtgacatc tcaaaaatcc ctgagggcga ctgtgtagta gttgccactg atgccttgtg 4500
tacagggtac actggtgact ttgattccgt gtatgactgc agcctcatgg tagaaggcac 4560
atgccatgtt gaccttgacc ctactttcac catgggtgtt cgtgtgtgcg gggtttcagc 4620

aatagttaaa ggccagcgta ggggccgcac aggccgtggg agagctggca tatactacta 4680
tgtagacggg agttgtaccc cttcgggtat ggttcctgaa tgcaacattg ttgaagcctt 4740
cgacgcagcc aaggcatggt atggtttgtc atcaacagaa gctcaaacta ttctggacac 4800
ctatcgcacc caacctgggt tacctgcgat aggagcaaat ttggacgagt gggctgatct 4860
cttttctatg gtcaaccccg aaccttcatt tgtcaatact gcaaaaagaa ctgctgacaa 4920
ttatgttttg ttgactgcag cccaactaca actgtgtcat cagtatggct atgctgctcc 4980
caatgacgca ccacggtggc agggagcccg gcttgggaaa aaaccttgtg gggttctgtg 5040
gcgcttggac ggcgctgacg cctgtcctgg cccagagccc agcgaggtga ccagatacca 5100
aatgtgcttc actgaagtca atacttctgg gacagccgca ctcgctgttg gcgttggagt 5160
ggctatggct tatctagcca ttgacacttt tggcgccact tgtgtgcggc gttgctggtc 5220
tattacatca gtccctaccg gtgctactgt cgccccagtg gttgacgaag aagaaatcgt 5280
ggaggagtgt gcatcattca ttcccttgga ggccatggtt gctgcaattg acaagctgaa 5340
gagtacaatc accacaacta gtcctttcac attggaaacc gcccttgaaa aacttaacac 5400
ctttcttggg cctcatgcag ctacaatcct tgctatcata gagtattgct gtggtttagt 5460
cactttacct gacaatccct ttgcatcatg cgtgtttgct ttcattgcgg gtattactac 5520
cccactacct cacaagatca aaatgttcct gtcattattt ggaggcgcaa ttgcgtccaa 5580
gcttacagac gctagaggcg cactggcgtt catgatggcc ggggctgcgg gaacagctct 5640
tggtacatgg acatcggtgg gttttgtctt tgacatgcta ggcggctatg ctgccgcctc 5700
atccactgct tgcttgacat ttaaatgctt gatgggtgag tggcccacta tggatcagct 5760
tgctggttta gtctactccg cgttcaatcc ggccgcagga gttgtgggcg tcttgtcagc 5820
ttgtgcaatg tttgctttga caacagcagg gccagatcac tggcccaaca gacttcttac 5880
tatgcttgct aggagcaaca ctgtatgtaa tgagtacttt attgccactc gtgacatccg 5940
caggaagata ctgggcattc tggaggcatc taccccctgg agtgtcatat cagcttgcat 6000
ccgttggctc cacaccccga cggaggatga ttgcggcctc attgcttggg gtctagagat 6060
ttggcagtat gtgtgcaatt tctttgtgat ttgctttaat gtccttaaag ctggagttca 6120
gagcatggtt aacattcctg gttgtccttt ctacagctgc cagaaggggt acaagggccc 6180
ctggattgga tcaggtatgc tccaagcacg ctgtccatgc ggtgctgaac tcatcttttc 6240
tgttgagaat ggttttgcaa aactttacaa aggacccaga acttgttcaa attactggag 6300
aggggctgtt ccagtcaacg ctaggctgtg tgggtcggct agaccggacc caactgattg 6360
gactagtctt gtcgtcaatt atggcgttag ggactactgt aaatatgaga aaatgggaga 6420
tcacattttt gttacagcag tatcctctcc aaatgtctgt ttcacccagg tgcccccaac 6480
cttgagagct gcagtggccg tggacggcgt acaggttcag tgttatctag gtgagcccaa 6540
aactccttgg acgacatctg cttgctgtta cggtcctgac ggtaagggta aaactgttaa 6600
gcttcccttc cgcgttgacg gtcacacacc tggtgtgcgc atgcaactta atttgcgtga 6660
tgcacttgag acaaatgact gtaattccac aaacaacact cctagtgatg aagccgcagt 6720
gtccgctctt gttttcaaac aggagttgcg gcgtacaaac caattgcttg aggcaatttc 6780
agctggcgtt gacaccacca aactgccagc cccctccatc gaagaggtag tggtaagaaa 6840
gcgccagttc cgggcaagaa ctggttcgct taccttgcct ccccctccga gatccgtccc 6900
aggagtgtca tgtcctgaaa gcctgcaacg aagtgacccg ttagaaggtc cttcaaacct 6960
ccctccttca ccacctgttc tacagttggc catgccgatg cccctgttgg gagcgggtga 7020
gtgtaaccct ttcactgcaa ttggatgtgc aatgaccgaa acaggcggag gccctgatga 7080
tttacccagt taccctccca aaaaggaggt ctctgaatgg tcagacgaaa gttggtcgac 7140
ggctacaacc gcttccagct acgttactgg ccccccgtac cctaagatac ggggaaagga 7200
ttccactcag tcagcccccg ccaaacggcc tacaaaaaag aagttgggaa agagtgagtt 7260
ttcgtgcagc atgagctaca cctggaccga cgtgattagc ttcaaaactg cttctaaagt 7320
tctgtctgca actcgggcca tcactagtgg tttcctcaaa caaagatcat tggtgtatgt 7380
gactgagccg cgggatgcgg agcttagaaa acaaaaagtc actattaata gacaacctct 7440
gttcccccca tcataccaca agcaagtgag attggctaag gaaaaagctt caaaagttgt 7500

cggtgtcatg tgggactatg atgaagtagc agctcacacg ccctctaagt ctgctaagtc 7560
ccacatcact ggccttcggg gcactgatgt tcgttctgga gcagcccgca aggctgttct 7620
ggacttgcag aagtgtgtcg aggcaggtga gataccgagt cattatcggc aaactgtgat 7680
agttccaaag gaggaggtct tcgtgaagac cccccagaaa ccaacaaaga aacccccaag 7740
gcttatctcg taccccccacc ttgaaatgag atgtgttgag aagatgtact acggtcaggt 7800
tgctcctgac gtagttaaag ctgtcatggg agatgcgtac gggtttgtag atccacgtac 7860
ccgtgtcaag cgtctgttgt cgatgtggtc acccgatgca gtcggagcca catgcgatac 7920
agtgtgtttt gacagtacca tcacacccga ggatatcatg gtggagacag acatctactc 7980
agcagctaaa ctcagtgacc aacaccgagc tggcattcac accattgcga ggcagttata 8040
cgctggagga ccgatgatcg cttatgatgg ccgagagatc ggatatcgta ggtgtaggtc 8100
ttccggcgtc tatactacct caagttccaa cagtttgacc tgctggctga aggtaaatgc 8160
tgcagccgaa caggctggca tgaagaaccc tcgcttcctt atttgcggcg atgattgcac 8220
cgtaatttgg aagagcgccg gagcagatgc agacaaacaa gcaatgcgtg tctttgctag 8280
ctggatgaag gtgatgggtg caccacaaga ttgtgtgcct caacccaaat acagtttgga 8340
agaattaaca tcatgctcat caaatgttac ctctggaatt accaaaagtg gcaagcctta 8400
ctactttctt acaagagatc ctcgtatccc ccttggcagg tgctctgccg agggtctggg 8460
atacaacccc agtgctgcgt ggattgggta tctaatacat cactacccat gtttgtgggt 8520
tagccgtgtg ttggctgtcc atttcatgga gcagatgctc tttgaggaca aacttcccga 8580
gactgtgacc tttgactggt atgggaaaaa ttatacggtg cctgtagaag atctgcccag 8640
catcattgct ggtgtgcacg gtattgaggc tttctcggtg gtgcgctaca ccaacgctga 8700
gatcctcaga gtttcccaat cactaacaga catgaccatg ccccccctgc gagcctggcg 8760
aaagaaagcc agggcggtcc tcgccagcgc caagaggcgt ggcggagcac acgcaaaatt 8820
ggctcgcttc cttctctggc atgctacatc tagacctcta ccagatttgg ataagacgag 8880
cgtggctcgg tacaccactt tcaattattg tgatgtttac tccccggagg gggatgtgtt 8940
tattacacca cagagaagat tgcagaagtt ccttgtgaag tatttggctg tcattgtttt 9000
tgccctaggg ctcattgctg ttggattagc catcagctga acccccaaat tcaaaattaa 9060
ctaacagttt ttttttttt ttttttttt agggcagcgg caacagggga gaccccgggc 9120
ttaacgaccc cgcgatgtg 9139

<210> 4
<211> 9711
<212> DNA
<213> Hepatitis C virus

<400> 4
acccgccccc aataggggcg acactccgcc atgaatcact cccctgtgag gaactactgt 60
cttcacgcag aaagcgtcta gccatggcgt tagtatgagt gtcgtacagc ctccaggccc 120
ccccctcccg ggagagccat agtggtctgc ggaaccggtg agtacaccgg aattgccggg 180
aagactgggt cctttcttgg ataaacccac tctatgcccg gccatttggg cgtgcccccg 240
caagactgct agccgagtag cgttgggttg cgaaaggcct tgtggtactg cctgataggg 300
tgcttgcgag tgccccggga ggtctcgtag accgtgcacc atgagcacaa atcctaaacc 360
tcaaagaaaa accaaaagaa acaccaaccg tcgcccacaa gacgttaagt ttccgggcgg 420
cggccagatc gttggcggag tatacttgtt gccgcgcagg ggccccaggt tgggtgtgcg 480
cgcgacaagg aagacttcgg agcggtccca gccacgtgga aggcgccagc ccatccctaa 540
agatcggcgc tccactggca aatcctgggg aaaaccagga tacccctggc ccctatacgg 600
gaatgaggga ctcggctggg caggatggct cctgtccccc cgaggttccc gtccctcttg 660
gggccccaat gacccccggc ataggtcgcg caacgtgggt aaggtcatcg ataccctaac 720

gtgcggcttt gccgacctca tggggtacat ccctgtcgtg ggcgccccgc tcggcggcgt 780
cgccagagct ctcgcgcatg gcgtgagagt cctggaggac ggggttaatt ttgcaacagg 840
gaacttaccc ggttgctcct tttctatctt cttgctggcc ctgctgtcct gcatcaccac 900
cccggtctcc gctgccgaag tgaagaacat cagtaccggc tacatggtga ctaacgactg 960
caccaatgac agcattacct ggcagctcca ggctgctgtc ctccacgtcc ccgggtgcgt 1020
cccgtgcgag aaagtgggga atgcatctca gtgctggata ccggtctcac cgaatgtggc 1080
cgtgcagcgg cccggcgccc tcacgcaggg cttgcggacg cacatcgaca tggttgtgat 1140
gtccgccacg ctctgctctg ccctctacgt gggggacctc tgcggtgggg tgatgctcgc 1200
agcccaaatg ttcattgtct cgccgcagca ccactggttt gtccaagact gcaattgctc 1260
catctaccct ggtaccatca ctggacaccg catggcatgg gacatgatga tgaactggtc 1320
gcccacggct accatgatct tggcgtacgc gatgcgtgtc cccgaggtca ttatagacat 1380
cattagcggg gctcattggg gcgtcatgtt cggcttggcc tacttctcta tgcagggagc 1440
gtgggcgaaa gtcgttgtca tccttctgtt ggccgccggg gtggacgcgc gcacccatac 1500
tgttgggggt tctgccgcgc agaccaccgg gcgcctcacc agcttatttg acatgggccc 1560
caggcagaaa atccagctcg ttaacaccaa tggcagctgg cacatcaacc gcaccgccct 1620
gaactgcaat gactccttgc acaccggctt tatcgcgtct ctgttctaca cccacagctt 1680
caactcgtca ggatgtcccg aacgcatgtc cgcctgccgc agtatcgagg ccttccgggt 1740
gggatggggc gccttgcaat atgaggataa tgtcaccaat ccagaggata tgagacccta 1800
ttgctggcac tacccaccaa ggcagtgtgg cgtggtctcc gcgaagactg tgtgtggccc 1860
agtgtactgt ttcaccccca gcccagtggt agtgggcacg accgacaggc ttggagcgcc 1920
cacttacacg tgggggggaga atgagacaga tgtcttccta ttgaacagca ctcgaccacc 1980
gctggggtca tggttcggct gcacgtggat gaactcttct ggctacacca agacttgcgg 2040
cgcaccaccc tgccgtacta gagctgactt caacgccagc acggacctgt tgtgccccac 2100
ggactgtttt aggaagcatc ctgataccac ttacctcaaa tgcggctctg ggccctggct 2160
cacgccaagg tgcctgatcg actaccccta caggctctgg cattaccccc gcacagttaa 2220
ctataccatc ttcaaaataa ggatgtatgt gggaggggtt gagcacaggc tcacggctgc 2280
atgcaatttc actcgtgggg atcgttgcaa cttggaggac agagacagaa gtcaactgtc 2340
tcctttgttg cactccacca cggaatgggc cattttacct tgctcttact cggacctgcc 2400
cgccttgtcg actggtcttc tccacctcca ccaaaacatc gtggacgtac aattcatgta 2460
tggcctatca cctgccctca caaaatacat cgtccgatgg gagtgggtaa tactcttatt 2520
cctgctctta gcggacgcca gggtttgcgc ctgcttatgg atgctcatct tgttgggcca 2580
ggccgaagca gcactagaga agctggtcat cttgcacgct gcgagcgcag ctagctgcaa 2640
tggcttccta tattttgtca tctttttcgt ggctgcttgg tacatcaagg gtcgggtagt 2700
ccccttagct acctattccc tcactggcct gtggtccttt agcctactgc tcctagcatt 2760
gccccaacag gcttatgctt atgacgcatc tgtgcatggc cagataggag cggctctgct 2820
ggtaatgatc actctcttta ctctcacccc cgggtataag acccttctca gccggttttt 2880
gtggtggttg tgctatcttc tgaccctggg ggaagctatg gtccaggagt gggcaccacc 2940
tatgcaggtg cgcggtggcc gtgatggcat catatgggcc gtcgccatat tctacccagg 3000
tgtggtgttt gacataacca agtggctctt ggcggtgctt gggcctgctt acctcctaaa 3060
aggtgctttg acgcgcgtgc cgtacttcgt cagggctcac gctctactga ggatgtgcac 3120
catggcaagg catctcgcgg ggggcaggta cgtccagatg gcgctactag cccttggcag 3180
gtggactggc acttacatct atgaccacct caccctatg tcggattggg ctgctagtgg 3240
cctgcgggac ctggcggtcg ccgttgagcc tatcatcttc agtccgatgg agaagaaagt 3300
cattgtctgg ggagcggaga cagctgcttg tggggacatt ttacacggac ttcccgtgtc 3360
cgcccgactt ggtcgggagg tcctccttgg cccagctgat ggctatacct ccaaggggtg 3420
gagtcttctc gcccccatca ctgcttacgc ccagcagaca cgtggccttt tgggcaccat 3480
agtggtgagc atgacggggc gcgacaagac agaacaggct ggggaaattc aggtcctgtc 3540
cacagtcact cagtccttcc tcggaacatc catctcgggg gttttgtgga ctgtctacca 3600

tggagctggc aacaagactc tggccggctc acggggtccg gtcacgcaga tgtactccag 3660
tgctgagggg gacttagtag ggtggcccag ccccccctggg actaaatctt tggagccgtg 3720
cacgtgtgga gcggtcgacc tgtacctggt cacgcggaac gctgatgtca tcccggctcg 3780
aagacgcggg gacaaacggg gagcgctact ctccccgaga cctctttcca ccttgaaggg 3840
gtcctcagga ggcccggtgc tatgccccag gggccacgct gtcggagtct tccgggcagc 3900
tgtgtgctct cggggcgtgg ctaagtccat agatttcatc cccgttgaga cactcgacat 3960
cgtcacgcgg tcccccacct ttagtgacaa cagcacacca cctgctgtgc cccagaccta 4020
tcaggtcggg tacttgcatg ccccgactgg cagtggaaag agcaccaaag ttcctgtcgc 4080
atatgctgct caggggtata aagtgctagt gcttaatccc tcagtggctg ccaccctggg 4140
gtttggggcg tacttgtcta aggcacatgg catcaatccc aacattagga ctggagtcag 4200
gactgtgacg accggggcgc ccatcacgta ctccacatat ggcaaattcc tcgccgatgg 4260
gggctgtgcg ggcggcgcct acgacatcat catatgtgat gaatgccatg ccgtggactc 4320
taccaccatc cttggcatcg gaacagtcct tgatcaagca gagacagctg gggtcagact 4380
aactgtgctg gctacagcta cgccccctgg gtcagtgaca acccccccacc ccaacataga 4440
ggaggtggcc cttgggcagg agggcgagat ccccttctat gggagggcga ttcccctgtc 4500
ttacatcaag ggaggaagac atctgatctt ctgccattca aagaaaaagt gtgacgagct 4560
cgcggcggcc cttcggggta tgggcttgaa ctcagtggca tactacagag ggttggacgt 4620
ctccgtaata ccaactcagg gagacgtagt ggtcgtcgcc accgacgccc tcatgacagg 4680
gtatactggg gactttgact ccgtgatcga ctgcaacgta gcggtcactc aagttgtaga 4740
cttcagttta gaccccacat tcaccataac cacacagatt gtccctcaag acgctgtctc 4800
acgtagccag cgccggggtc gcacgggtag gggaagactg ggcatttata ggtatgtttc 4860
cactggtgag cgagcctcag gaatgtttga cagtgtagtg ctctgtgagt gctacgacgc 4920
aggggccgca tggtatgagc tcacaccatc ggagaccacc gtcaggctca gggcgtattt 4980
caacacgccc ggtttgcctg tgtgccaaga ccatcttgag ttttgggagg cagttttcac 5040
cggcctcaca cacatagatg cccacttcct ttcccaaaca aagcaatcgg gggaaaattt 5100
cgcatactta acagcctacc aggctacagt gtgcgctagg gccaaagccc ccccccgtc 5160
ctgggacgtc atgtggaagt gtttgactcg actcaagccc acactcgtgg gccccacacc 5220
tctcctgtac cgcttgggct ctgttaccaa cgaggtcacc ctcacacatc ccgtgacgaa 5280
atacatcgcc acctgcatgc aagccgacct tgaggtcatg accagcacat gggtcttggc 5340
aggggagtc ttggcggccg tcgccgcgta ttgcctggcg accgggtgtg tttgcatcat 5400
cggccgcttg cacattaacc agcgagccgt cgttgcgccg gacaaggagg tcctctatga 5460
ggcttttgat gagatggagg aatgtgcctc tagggcggct ctcattgaag aggggcagcg 5520
gatagccgag atgctgaagt ccaagatcca aggcttattg cagcaagctt ccaaacaagc 5580
tcaagacata caacccactg tgcaggcttc atggcccaag gtagaacaat tctgggccaa 5640
acacatgtgg aacttcatta gcggcatcca atacctcgca ggactatcaa cactgccagg 5700
gaaccctgca gtagcttcca tgatggcgtt cagtgccgcc ctcaccagtc cgctgtcaac 5760
aagcaccact atccttctca acattttggg gggctggcta gcatcccaaa ttgcaccacc 5820
cgcgggggcc actggcttcg ttgtcagtgg cctagtggga gctgccgtag gcagtatagg 5880
cttaggtaag gtgctagtgg acatcctggc agggtatggt gcgggcattt cgggggctct 5940
cgtcgcattc aagatcatgt ctggcgagaa gccctccatg gaggatgtcg tcaacttgct 6000
gcctggaatt ctgtctccgg gtgccttggt agtgggagtc atctgcgcgg ccattctgcg 6060
ccgacacgtg ggaccggggg aaggcgccgt ccaatggatg aatagactca ttgcctttgc 6120
ttccagagga aatcacgtcg cccccaccca ctacgtgacg gagtcggatg cgtcgcagcg 6180
tgtgacccaa ctacttggct cccttaccat aaccagcctg ctcagaagac tccacaactg 6240
gattactgag gactgcccca tcccatgcgg cggctcgtgg ctccgcgatg tgtgggactg 6300
ggtttgcacc atcctaacag actttaaaaa ttggctgacc tccaaattat tcccaaagat 6360
gcccggcctc ccctttgtct cctgtcaaaa ggggtacaag ggcgtgtggg ccggcactgg 6420
catcatgacc acacggtgtc cttgcggcgc caatatctct ggcaatgtcc gcttgggctc 6480

catgagaatc acggggccta agacctgcat gaatatctgg caggggacct ttcctatcaa 6540
ttgttacacg gagggccagt gcgtgccgaa acccgcgcca aactttaagg tcgccatctg 6600
gagggtggcg gcctcagagt acgcggaggt gacgcagcac gggtcatacc actacataac 6660
aggactcacc actgataact tgaaagtccc ctgccaacta ccctctcccg agttcttttc 6720
ctgggtggac ggagtgcaga tccataggtt tgcccccaca ccgaagccgt ttttccggga 6780
tgaggtctcg ttctgcgttg ggcttaattc atttgtcgtc gggtcccagc ttccttgcga 6840
ccctgaaccc gacacagacg tattgatgtc catgctaaca gatccatctc atatcacggc 6900
ggagactgca gcgcggcgtt tagcgcgggg gtcaccccca tccgaggcaa gctcctcggc 6960
gagccagcta tcggcaccat cgctgcgagc cacctgcacc acccacggca aagcctatga 7020
tgtggacatg gtggatgcta acctgttcat ggggggcgat gtgactcgga tagagtctgg 7080
gtccaaagtg gtcgttctgg actctctcga cccaatggtc gaagaaagga gcgaccttga 7140
gccttcgata ccatcagaat acatgctccc caagaagagg ttcccaccag ctttaccggc 7200
ctgggcacgg cctgattaca acccaccgct tgtggaatcg tggaaaaggc cagattacca 7260
accggccact gttgcgggct gtgctctccc tcctcctagg aaaaccccga cgcctccccc 7320
aaggaggcgc cggacagtgg gcctaagtga ggactccata ggagatgccc ttcaacagct 7380
ggccattaag tcctttggcc agccccccc aagcggcgat tcaggccttt ccacgggggc 7440
gggcgctgcc gattccggca gtcagacgcc tcctgatgag ttggcccttt cggagacagg 7500
ttccatctct tccatgcccc ccctcgaggg ggagcttgga gatccagacc tggagcctga 7560
gcaggtagag ccccaacccc ccccccaggg gggggtggca gctcccggct cggactcggg 7620
gtcctggtct acttgctccg aggaggacga ctccgtcgtg tgctgctcca tgtcatactc 7680
ctggaccggg gctctaataa ctccttgtag tcccgaagag gagaagttac cgattaaccc 7740
cttgagcaac tccctgttgc gatatcacaa caaggtgtac tgtaccacaa caaagagcgc 7800
ctcactaagg gctaaaaagg taacttttga taggatgcaa gtgctcgact cctactacga 7860
ctcagtctta aaggacatta agctagcggc ctccaaggtc accgcaaggc tcctcaccat 7920
ggaggaggct tgccagttaa ccccacccca ttctgcaaga tctaaatatg ggtttggggc 7980
taaggaggtc cgcagcttgt ccgggagggc cgttaaccac atcaagtccg tgtggaagga 8040
cctcctggag gactcagaaa caccaattcc cacaaccatt atggccaaaa atgaggtgtt 8100
ctgcgtggac cccaccaagg ggggcaagaa agcagctcgc cttatcgttt accctgacct 8160
cggcgtcagg gtctgcgaga agatggccct ttatgacatt acacaaaaac ttcctcaggc 8220
ggtgatgggg gcttcttatg gattccagta ttcccccgct cagcgggtag agtttctctt 8280
gaaagcatgg gcggaaaaga aggaccctat gggtttttcg tatgataccc gatgctttga 8340
ctcaaccgtc actgagagag acatcaggac tgaggagtcc atatatcggg cctgctcctt 8400
gcccgaggag gcccacactg ccatacactc gctaactgag agactttacg tgggagggcc 8460
tatgttcaac agcaagggcc aaacctgcgg gtacaggcgt tgccgcgcca gcggggtgct 8520
caccactagc atggggaaca ccatcacatg ctacgtgaaa gccttagcgg cttgtaaagc 8580
tgcagggata atcgcgccca caatgctggt atgcggcgat gacttggttg tcatctcaga 8640
aagccagggg accgaggagg acgagcggaa cctgagagcc ttcacggagg ctatgaccag 8700
gtattctgcc cctcctggtg acccccccag accggagtat gatctggagc tgataacatc 8760
ttgctcctca aatgtgtctg tggcgctggg cccacaaggc cgccgcagat actacctgac 8820
cagagaccct accactccaa tcgcccgggc tgcctgggaa acagttagac actcccctgt 8880
caattcatgg ctgggaaaca tcatccagta cgccccgacc atatgggctc gcatggtcct 8940
gatgacacac ttcttctcca ttctcatggc tcaagacacg ctggaccaga acctcaactt 9000
tgagatgtac ggagcggtgt actccgtgag tcccttggac ctcccagcta taattgaaag 9060
gttacatggg cttgacgctt tttctctgca cacatacact ccccacgaac tgacacgggt 9120
ggcttcagcc ctcagaaaac ttggggcgcc acccctcaga gcgtggaaga gccgggcacg 9180
tgcagtcagg gcgtccctca tctcccgtgg ggggagagcg gccgtttgcg gtcgatatct 9240
cttcaattgg gcggtgaaga ccaagctcaa actcactcca ttgccggaag cgcgcctcct 9300
ggatttatcc agctggttca ccgtcggcgc cggcgggggc gacatttatc acagcgtgtc 9360

gcgtgcccga ccccgcttat tgctctttgg cctactccta ctttttgtag gggtaggcct 9420
tttcctactc cccgctcggt agagcggcac acattagcta cactccatag ctaactgtcc 9480
ctttttttct ttttttttct ttttttttct ttttttttct ttttttttct ttttttttct 9540
ttttttttct ttttttttct ttttctcttt tttctctttt ccttctttct taccttattt 9600
tactttcttt cctggtggct ccatcttagc cctagtcacg gctagctgtg aaaggtccgt 9660
gagccgcatg actgcagaga gtgccgtaac tggtctctct gcagatcatg t 9711

<210> 5
<211> 3033
<212> PRT
<213> Hepatitis C virus

<400> 5

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn
1 5 10 15

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly
20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
35 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
50 55 60

Ile Pro Lys Asp Arg Arg Ser Thr Gly Lys Ser Trp Gly Lys Pro Gly
65 70 75 80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp
85 90 95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
100 105 110

Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
130 135 140

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
145 150 155 160

Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
165 170 175

Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala

```
            180                 185                 190

Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
        195                 200                 205

Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
    210                 215                 220

Gly Cys Val Pro Cys Glu Lys Val Gly Asn Ala Ser Gln Cys Trp Ile
225                 230                 235                 240

Pro Val Ser Pro Asn Val Ala Val Gln Arg Pro Gly Ala Leu Thr Gln
                245                 250                 255

Gly Leu Arg Thr His Ile Asp Met Val Val Met Ser Ala Thr Leu Cys
            260                 265                 270

Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Met Leu Ala Ala
        275                 280                 285

Gln Met Phe Ile Val Ser Pro Gln His His Trp Phe Val Gln Asp Cys
    290                 295                 300

Asn Cys Ser Ile Tyr Pro Gly Thr Ile Thr Gly His Arg Met Ala Trp
305                 310                 315                 320

Asp Met Met Met Asn Trp Ser Pro Thr Ala Thr Met Ile Leu Ala Tyr
                325                 330                 335

Ala Met Arg Val Pro Glu Val Ile Ile Asp Ile Ile Ser Gly Ala His
            340                 345                 350

Trp Gly Val Met Phe Gly Leu Ala Tyr Phe Ser Met Gln Gly Ala Trp
        355                 360                 365

Ala Lys Val Val Val Ile Leu Leu Leu Ala Ala Gly Val Asp Ala Arg
    370                 375                 380

Thr His Thr Val Gly Gly Ser Ala Ala Gln Thr Thr Gly Arg Leu Thr
385                 390                 395                 400

Ser Leu Phe Asp Met Gly Pro Arg Gln Lys Ile Gln Leu Val Asn Thr
                405                 410                 415

Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu Asn Cys Asn Asp Ser
            420                 425                 430

Leu His Thr Gly Phe Ile Ala Ser Leu Phe Tyr Thr His Ser Phe Asn
```

435 440 445

Ser Ser Gly Cys Pro Glu Arg Met Ser Ala Cys Arg Ser Ile Glu Ala
450 455 460

Phe Arg Val Gly Trp Gly Ala Leu Gln Tyr Glu Asp Asn Val Thr Asn
465 470 475 480

Pro Glu Asp Met Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Gln Cys
485 490 495

Gly Val Val Ser Ala Lys Thr Val Cys Gly Pro Val Tyr Cys Phe Thr
500 505 510

Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Leu Gly Ala Pro Thr
515 520 525

Tyr Thr Trp Gly Glu Asn Glu Thr Asp Val Phe Leu Leu Asn Ser Thr
530 535 540

Arg Pro Pro Leu Gly Ser Trp Phe Gly Cys Thr Trp Met Asn Ser Ser
545 550 555 560

Gly Tyr Thr Lys Thr Cys Gly Ala Pro Pro Cys Arg Thr Arg Ala Asp
565 570 575

Phe Asn Ala Ser Thr Asp Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys
580 585 590

His Pro Asp Thr Thr Tyr Leu Lys Cys Gly Ser Gly Pro Trp Leu Thr
595 600 605

Pro Arg Cys Leu Ile Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys
610 615 620

Thr Val Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val
625 630 635 640

Glu His Arg Leu Thr Ala Ala Cys Asn Phe Thr Arg Gly Asp Arg Cys
645 650 655

Asn Leu Glu Asp Arg Asp Arg Ser Gln Leu Ser Pro Leu Leu His Ser
660 665 670

Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala
675 680 685

Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln

690 695 700

Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
705 710 715 720

Glu Trp Val Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys
725 730 735

Ala Cys Leu Trp Met Leu Ile Leu Leu Gly Gln Ala Glu Ala Ala Leu
740 745 750

Glu Lys Leu Val Ile Leu His Ala Ala Ser Ala Ala Ser Cys Asn Gly
755 760 765

Phe Leu Tyr Phe Val Ile Phe Phe Val Ala Ala Trp Tyr Ile Lys Gly
770 775 780

Arg Val Val Pro Leu Ala Thr Tyr Ser Leu Thr Gly Leu Trp Ser Phe
785 790 795 800

Ser Leu Leu Leu Leu Ala Leu Pro Gln Gln Ala Tyr Ala Tyr Asp Ala
805 810 815

Ser Val His Gly Gln Ile Gly Ala Ala Leu Leu Val Met Ile Thr Leu
820 825 830

Phe Thr Leu Thr Pro Gly Tyr Lys Thr Leu Leu Ser Arg Phe Leu Trp
835 840 845

Trp Leu Cys Tyr Leu Leu Thr Leu Gly Glu Ala Met Val Gln Glu Trp
850 855 860

Ala Pro Pro Met Gln Val Arg Gly Gly Arg Asp Gly Ile Ile Trp Ala
865 870 875 880

Val Ala Ile Phe Tyr Pro Gly Val Val Phe Asp Ile Thr Lys Trp Leu
885 890 895

Leu Ala Val Leu Gly Pro Ala Tyr Leu Leu Lys Gly Ala Leu Thr Arg
900 905 910

Val Pro Tyr Phe Val Arg Ala His Ala Leu Leu Arg Met Cys Thr Met
915 920 925

Ala Arg His Leu Ala Gly Gly Arg Tyr Val Gln Met Ala Leu Leu Ala
930 935 940

Leu Gly Arg Trp Thr Gly Thr Tyr Ile Tyr Asp His Leu Thr Pro Met

945 950 955 960

Ser Asp Trp Ala Ala Ser Gly Leu Arg Asp Leu Ala Val Ala Val Glu
965 970 975

Pro Ile Ile Phe Ser Pro Met Glu Lys Lys Val Ile Val Trp Gly Ala
980 985 990

Glu Thr Ala Ala Cys Gly Asp Ile Leu His Gly Leu Pro Val Ser Ala
995 1000 1005

Arg Leu Gly Arg Glu Val Leu Leu Gly Pro Ala Asp Gly Tyr Thr Ser
1010 1015 1020

Lys Gly Trp Ser Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr
1025 1030 1035 1040

Arg Gly Leu Leu Gly Thr Ile Val Val Ser Met Thr Gly Arg Asp Lys
1045 1050 1055

Thr Glu Gln Ala Gly Glu Ile Gln Val Leu Ser Thr Val Thr Gln Ser
1060 1065 1070

Phe Leu Gly Thr Ser Ile Ser Gly Val Leu Trp Thr Val Tyr His Gly
1075 1080 1085

Ala Gly Asn Lys Thr Leu Ala Gly Ser Arg Gly Pro Val Thr Gln Met
1090 1095 1100

Tyr Ser Ser Ala Glu Gly Asp Leu Val Gly Trp Pro Ser Pro Pro Gly
1105 1110 1115 1120

Thr Lys Ser Leu Glu Pro Cys Thr Cys Gly Ala Val Asp Leu Tyr Leu
1125 1130 1135

Val Thr Arg Asn Ala Asp Val Ile Pro Ala Arg Arg Arg Gly Asp Lys
1140 1145 1150

Arg Gly Ala Leu Leu Ser Pro Arg Pro Leu Ser Thr Leu Lys Gly Ser
1155 1160 1165

Ser Gly Gly Pro Val Leu Cys Pro Arg Gly His Ala Val Gly Val Phe
1170 1175 1180

Arg Ala Ala Val Cys Ser Arg Gly Val Ala Lys Ser Ile Asp Phe Ile
1185 1190 1195 1200

Pro Val Glu Thr Leu Asp Ile Val Thr Arg Ser Pro Thr Phe Ser Asp

1205 1210 1215

Asn Ser Thr Pro Pro Ala Val Pro Gln Thr Tyr Gln Val Gly Tyr Leu
1220 1225 1230

His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Val Ala Tyr
1235 1240 1245

Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala
1250 1255 1260

Thr Leu Gly Phe Gly Ala Tyr Leu Ser Lys Ala His Gly Ile Asn Pro
1265 1270 1275 1280

Asn Ile Arg Thr Gly Val Arg Thr Val Thr Thr Gly Ala Pro Ile Thr
1285 1290 1295

Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ala Gly Gly
1300 1305 1310

Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ala Val Asp Ser Thr
1315 1320 1325

Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly
1330 1335 1340

Val Arg Leu Thr Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr
1345 1350 1355 1360

Thr Pro His Pro Asn Ile Glu Glu Val Ala Leu Gly Gln Glu Gly Glu
1365 1370 1375

Ile Pro Phe Tyr Gly Arg Ala Ile Pro Leu Ser Tyr Ile Lys Gly Gly
1380 1385 1390

Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala
1395 1400 1405

Ala Ala Leu Arg Gly Met Gly Leu Asn Ser Val Ala Tyr Tyr Arg Gly
1410 1415 1420

Leu Asp Val Ser Val Ile Pro Thr Gln Gly Asp Val Val Val Val Ala
1425 1430 1435 1440

Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile
1445 1450 1455

Asp Cys Asn Val Ala Val Thr Gln Val Val Asp Phe Ser Leu Asp Pro

1460 1465 1470

Thr Phe Thr Ile Thr Thr Gln Ile Val Pro Gln Asp Ala Val Ser Arg
1475 1480 1485

Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Leu Gly Ile Tyr Arg
1490 1495 1500

Tyr Val Ser Thr Gly Glu Arg Ala Ser Gly Met Phe Asp Ser Val Val
1505 1510 1515 1520

Leu Cys Glu Cys Tyr Asp Ala Gly Ala Ala Trp Tyr Glu Leu Thr Pro
1525 1530 1535

Ser Glu Thr Thr Val Arg Leu Arg Ala Tyr Phe Asn Thr Pro Gly Leu
1540 1545 1550

Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ala Val Phe Thr Gly
1555 1560 1565

Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly
1570 1575 1580

Glu Asn Phe Ala Tyr Leu Thr Ala Tyr Gln Ala Thr Val Cys Ala Arg
1585 1590 1595 1600

Ala Lys Ala Pro Pro Pro Ser Trp Asp Val Met Trp Lys Cys Leu Thr
1605 1610 1615

Arg Leu Lys Pro Thr Leu Val Gly Pro Thr Pro Leu Leu Tyr Arg Leu
1620 1625 1630

Gly Ser Val Thr Asn Glu Val Thr Leu Thr His Pro Val Thr Lys Tyr
1635 1640 1645

Ile Ala Thr Cys Met Gln Ala Asp Leu Glu Val Met Thr Ser Thr Trp
1650 1655 1660

Val Leu Ala Gly Gly Val Leu Ala Ala Val Ala Ala Tyr Cys Leu Ala
1665 1670 1675 1680

Thr Gly Cys Val Cys Ile Ile Gly Arg Leu His Ile Asn Gln Arg Ala
1685 1690 1695

Val Val Ala Pro Asp Lys Glu Val Leu Tyr Glu Ala Phe Asp Glu Met
1700 1705 1710

Glu Glu Cys Ala Ser Arg Ala Ala Leu Ile Glu Glu Gly Gln Arg Ile

```
      1715                1720                1725

Ala Glu Met Leu Lys Ser Lys Ile Gln Gly Leu Leu Gln Gln Ala Ser
   1730                1735                1740

Lys Gln Ala Gln Asp Ile Gln Pro Thr Val Gln Ala Ser Trp Pro Lys
1745                1750                1755                1760

Val Glu Gln Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile
               1765                1770                1775

Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Val Ala
           1780                1785                1790

Ser Met Met Ala Phe Ser Ala Ala Leu Thr Ser Pro Leu Ser Thr Ser
       1795                1800                1805

Thr Thr Ile Leu Leu Asn Ile Leu Gly Gly Trp Leu Ala Ser Gln Ile
   1810                1815                1820

Ala Pro Pro Ala Gly Ala Thr Gly Phe Val Val Ser Gly Leu Val Gly
1825                1830                1835                1840

Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val Asp Ile Leu
               1845                1850                1855

Ala Gly Tyr Gly Ala Gly Ile Ser Gly Ala Leu Val Ala Phe Lys Ile
           1860                1865                1870

Met Ser Gly Glu Lys Pro Ser Met Glu Asp Val Val Asn Leu Leu Pro
       1875                1880                1885

Gly Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Ile Cys Ala Ala
   1890                1895                1900

Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met
1905                1910                1915                1920

Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ala Pro Thr
               1925                1930                1935

His Tyr Val Thr Glu Ser Asp Ala Ser Gln Arg Val Thr Gln Leu Leu
           1940                1945                1950

Gly Ser Leu Thr Ile Thr Ser Leu Leu Arg Arg Leu His Asn Trp Ile
       1955                1960                1965

Thr Glu Asp Cys Pro Ile Pro Cys Gly Gly Ser Trp Leu Arg Asp Val
```

1970 1975 1980

Trp Asp Trp Val Cys Thr Ile Leu Thr Asp Phe Lys Asn Trp Leu Thr
1985 1990 1995 2000

Ser Lys Leu Phe Pro Lys Met Pro Gly Leu Pro Phe Val Ser Cys Gln
2005 2010 2015

Lys Gly Tyr Lys Gly Val Trp Ala Gly Thr Gly Ile Met Thr Thr Arg
2020 2025 2030

Cys Pro Cys Gly Ala Asn Ile Ser Gly Asn Val Arg Leu Gly Ser Met
2035 2040 2045

Arg Ile Thr Gly Pro Lys Thr Cys Met Asn Ile Trp Gln Gly Thr Phe
2050 2055 2060

Pro Ile Asn Cys Tyr Thr Glu Gly Gln Cys Val Pro Lys Pro Ala Pro
2065 2070 2075 2080

Asn Phe Lys Val Ala Ile Trp Arg Val Ala Ala Ser Glu Tyr Ala Glu
2085 2090 2095

Val Thr Gln His Gly Ser Tyr His Tyr Ile Thr Gly Leu Thr Thr Asp
2100 2105 2110

Asn Leu Lys Val Pro Cys Gln Leu Pro Ser Pro Glu Phe Phe Ser Trp
2115 2120 2125

Val Asp Gly Val Gln Ile His Arg Phe Ala Pro Thr Pro Lys Pro Phe
2130 2135 2140

Phe Arg Asp Glu Val Ser Phe Cys Val Gly Leu Asn Ser Phe Val Val
2145 2150 2155 2160

Gly Ser Gln Leu Pro Cys Asp Pro Glu Pro Asp Thr Asp Val Leu Met
2165 2170 2175

Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr Ala Ala Arg
2180 2185 2190

Arg Leu Ala Arg Gly Ser Pro Pro Ser Glu Ala Ser Ser Ser Ala Ser
2195 2200 2205

Gln Leu Ser Ala Pro Ser Leu Arg Ala Thr Cys Thr Thr His Gly Lys
2210 2215 2220

Ala Tyr Asp Val Asp Met Val Asp Ala Asn Leu Phe Met Gly Gly Asp

2225 2230 2235 2240

Val Thr Arg Ile Glu Ser Gly Ser Lys Val Val Val Leu Asp Ser Leu
2245 2250 2255

Asp Pro Met Val Glu Glu Arg Ser Asp Leu Glu Pro Ser Ile Pro Ser
2260 2265 2270

Glu Tyr Met Leu Pro Lys Lys Arg Phe Pro Pro Ala Leu Pro Ala Trp
2275 2280 2285

Ala Arg Pro Asp Tyr Asn Pro Pro Leu Val Glu Ser Trp Lys Arg Pro
2290 2295 2300

Asp Tyr Gln Pro Ala Thr Val Ala Gly Cys Ala Leu Pro Pro Pro Arg
2305 2310 2315 2320

Lys Thr Pro Thr Pro Pro Pro Arg Arg Arg Arg Thr Val Gly Leu Ser
2325 2330 2335

Glu Asp Ser Ile Gly Asp Ala Leu Gln Gln Leu Ala Ile Lys Ser Phe
2340 2345 2350

Gly Gln Pro Pro Pro Ser Gly Asp Ser Gly Leu Ser Thr Gly Ala Gly
2355 2360 2365

Ala Ala Asp Ser Gly Ser Gln Thr Pro Pro Asp Glu Leu Ala Leu Ser
2370 2375 2380

Glu Thr Gly Ser Ile Ser Ser Met Pro Pro Leu Glu Gly Glu Leu Gly
2385 2390 2395 2400

Asp Pro Asp Leu Glu Pro Glu Gln Val Glu Pro Gln Pro Pro Pro Gln
2405 2410 2415

Gly Gly Val Ala Ala Pro Gly Ser Asp Ser Gly Ser Trp Ser Thr Cys
2420 2425 2430

Ser Glu Glu Asp Asp Ser Val Val Cys Cys Ser Met Ser Tyr Ser Trp
2435 2440 2445

Thr Gly Ala Leu Ile Thr Pro Cys Ser Pro Glu Glu Glu Lys Leu Pro
2450 2455 2460

Ile Asn Pro Leu Ser Asn Ser Leu Leu Arg Tyr His Asn Lys Val Tyr
2465 2470 2475 2480

Cys Thr Thr Thr Lys Ser Ala Ser Leu Arg Ala Lys Lys Val Thr Phe

2485 2490 2495

Asp Arg Met Gln Val Leu Asp Ser Tyr Tyr Asp Ser Val Leu Lys Asp
2500 2505 2510

Ile Lys Leu Ala Ala Ser Lys Val Thr Ala Arg Leu Leu Thr Met Glu
2515 2520 2525

Glu Ala Cys Gln Leu Thr Pro Pro His Ser Ala Arg Ser Lys Tyr Gly
2530 2535 2540

Phe Gly Ala Lys Glu Val Arg Ser Leu Ser Gly Arg Ala Val Asn His
2545 2550 2555 2560

Ile Lys Ser Val Trp Lys Asp Leu Leu Glu Asp Ser Glu Thr Pro Ile
2565 2570 2575

Pro Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Asp Pro Thr
2580 2585 2590

Lys Gly Gly Lys Lys Ala Ala Arg Leu Ile Val Tyr Pro Asp Leu Gly
2595 2600 2605

Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Ile Thr Gln Lys Leu
2610 2615 2620

Pro Gln Ala Val Met Gly Ala Ser Tyr Gly Phe Gln Tyr Ser Pro Ala
2625 2630 2635 2640

Gln Arg Val Glu Phe Leu Leu Lys Ala Trp Ala Glu Lys Lys Asp Pro
2645 2650 2655

Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
2660 2665 2670

Arg Asp Ile Arg Thr Glu Glu Ser Ile Tyr Arg Ala Cys Ser Leu Pro
2675 2680 2685

Glu Glu Ala His Thr Ala Ile His Ser Leu Thr Glu Arg Leu Tyr Val
2690 2695 2700

Gly Gly Pro Met Phe Asn Ser Lys Gly Gln Thr Cys Gly Tyr Arg Arg
2705 2710 2715 2720

Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Met Gly Asn Thr Ile Thr
2725 2730 2735

Cys Tyr Val Lys Ala Leu Ala Ala Cys Lys Ala Ala Gly Ile Ile Ala

2740 2745 2750

Pro Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Ser Glu Ser
2755 2760 2765

Gln Gly Thr Glu Glu Asp Glu Arg Asn Leu Arg Ala Phe Thr Glu Ala
2770 2775 2780

Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Arg Pro Glu Tyr
2785 2790 2795 2800

Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala Leu
2805 2810 2815

Gly Pro Gln Gly Arg Arg Arg Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
2820 2825 2830

Pro Ile Ala Arg Ala Ala Trp Glu Thr Val Arg His Ser Pro Val Asn
2835 2840 2845

Ser Trp Leu Gly Asn Ile Ile Gln Tyr Ala Pro Thr Ile Trp Ala Arg
2850 2855 2860

Met Val Leu Met Thr His Phe Phe Ser Ile Leu Met Ala Gln Asp Thr
2865 2870 2875 2880

Leu Asp Gln Asn Leu Asn Phe Glu Met Tyr Gly Ala Val Tyr Ser Val
2885 2890 2895

Ser Pro Leu Asp Leu Pro Ala Ile Ile Glu Arg Leu His Gly Leu Asp
2900 2905 2910

Ala Phe Ser Leu His Thr Tyr Thr Pro His Glu Leu Thr Arg Val Ala
2915 2920 2925

Ser Ala Leu Arg Lys Leu Gly Ala Pro Pro Leu Arg Ala Trp Lys Ser
2930 2935 2940

Arg Ala Arg Ala Val Arg Ala Ser Leu Ile Ser Arg Gly Gly Arg Ala
2945 2950 2955 2960

Ala Val Cys Gly Arg Tyr Leu Phe Asn Trp Ala Val Lys Thr Lys Leu
2965 2970 2975

Lys Leu Thr Pro Leu Pro Glu Ala Arg Leu Leu Asp Leu Ser Ser Trp
2980 2985 2990

Phe Thr Val Gly Ala Gly Gly Gly Asp Ile Tyr His Ser Val Ser Arg

2995 3000 3005

Ala Arg Pro Arg Leu Leu Leu Phe Gly Leu Leu Leu Leu Phe Val Gly
3010 3015 3020

Val Gly Leu Phe Leu Leu Pro Ala Arg
3025 3030

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 00/15293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/51 C07K14/18 C12Q1/68 C12N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17) page 4, line 18 -page 6, line 17 page 55, line 24 -page 56, line 19 page 76; example 5 page 89, line 18 -page 96 page 109; example 15 page 148; example 21 page 427, line 17 -page 432 claims --- -/--	1,2,4-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2000	31/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCARSELLI ELISA ET AL: "GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity." JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, XP002150190 ISSN: 0022-538X cited in the application the whole document ---	19,24-26
A	HONDA MASAO ET AL: "A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation." JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, XP002150191 ISSN: 0022-538X cited in the application the whole document ---	19,22,23
A	YANAGI MASAYUKI ET AL: "In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, XP002150192 ISSN: 0027-8424 cited in the application ---	
A	YANAGI M ET AL: "Transcripts of a chimeric cDNA clone of hepatitis C virus genotype 1b are infectious in vivo" VIROLOGY, vol. 244, no. 1, 1998, pages 161-172, XP002089701 ISSN: 0042-6822 cited in the application ---	
P,X	BUKH JENS ET AL: "Toward a surrogate model for hepatitis C virus: An infectious molecular clone of the GB virus-B hepatitis agent." VIROLOGY, vol. 262, no. 2, 30 September 1999 (1999-09-30), pages 470-478, XP002150193 ISSN: 0042-6822 the whole document --- -/--	1-16,19

1

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/15293

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	SBARDELLATI ANDREA ET AL: "Identification of a novel sequence at the 3' end of the GB virus B genome." JOURNAL OF VIROLOGY, vol. 73, no. 12, December 1999 (1999-12), pages 10546-10550, XP002150194 ISSN: 0022-538X the whole document ---	1-16,19
P,X	BUTKIEWICZ N. ET AL.: "Virus-specific cofactor requirement and chimeric hepatitis C virus/GB virus B nonstructural protein 3." J VIROL 2000 MAY;74(9):4291-301, XP002150195 the whole document -----	19, 24-26, 33-35, 37,39

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/US 00/15293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521922 A	17-08-1995	CA 2166313 A	17-08-1995
		EP 0745129 A	04-12-1996
		JP 10337193 A	22-12-1998
		JP 9511137 T	11-11-1997
		US 5981172 A	09-11-1999
		US 5843450 A	01-12-1998
		US 6051374 A	18-04-2000
		WO 9829747 A	09-07-1998